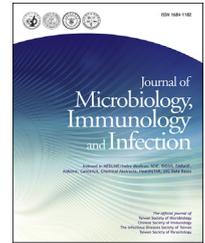




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Original Article

Human parvovirus B19 infection in patients with or without underlying diseases



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Received 5 July 2018; received in revised form 1 April 2019; accepted 15 May 2019

Available online 19 June 2019

KEYWORDS

Human parvovirus B19;
Erythema infectiosum;
Aplastic crisis;
Pure red-cell aplasia

Abstract *Background/Purpose:* The clinical presentations of parvovirus B19 in patients with underlying diseases have greater diversity than previously healthy patients. We retrospectively identified patients with polymerase chain reaction (PCR)-confirmed parvovirus B19 infection in attempt to describe its clinical features especially in these populations.

Methods: From 2009 to 2018, patients with real-time PCR-confirmed parvovirus B19 infection were collected. Comparisons were done between previously healthy patients and patients with preexisting diseases, as well as patients with high ($>5.5 \times 10^5$ copies/mL sera) and low viral loads.

Results: Parvovirus B19 DNA was detected in 31 patients. Fourteen (45%) patients had underlying diseases, including six (19%) with immunologic diseases, five (16%) with hematologic diseases, and three (10%) with cardiopulmonary diseases. Only seven (23%) patients received an initial impression of erythema infectiosum prior to positive PCR. A higher proportion of patients with underlying diseases presented with fatigue and pallor, and suffered from tachycardia and hepatosplenomegaly compared to previously healthy patients. Among patients with a high viral load, a substantial proportion were of older age, suffered fatigue, and anemia. There was a trend of patients with immunologic comorbidity having a higher viral load. *Conclusion:* The classical parvovirus B19 manifestations were less frequently observed in patients with a preexisting disease compared with previously healthy patients. Depending on host factors, the symptoms of parvovirus B19 infection can be multifaceted.

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Introduction

Since its discovery in 1975, human parvovirus B19, a member of the *Parvoviridae* family, has been known to cause mild and self-limiting diseases including erythema infectiosum (fifth disease)¹ and arthropathy in previously healthy subjects.² The virus displays remarkable tropism for human erythroid progenitor cells. As such, it also causes acute anemia by aplastic crisis in patients with shortened red cell survival,^{2,3} chronic viremia with or without anemia in immunocompromised patients, and hydrops fetalis or intrauterine death in infected fetuses.^{1,2}

Parvovirus B19 is active worldwide with neither ethnical nor geographical boundaries, albeit with some regional differences.⁴ Generally, seropositivity is lowest among young children, rises to around 50% at puberty,⁵ and increases further at lower rates throughout adulthood.⁴ Seropositivity is correlated with age, a history of transfusion, and urban residency.⁶ Transmission of parvovirus B19 occurs via respiratory droplets, vertical transmission from mother to fetus, and solid-organ or bone marrow transplants.⁴

Traditionally, laboratory diagnosis of parvovirus B19 infection relies on serologic and DNA tests.² IgM antibodies appear one week post-infection³ and persist for two to three months.^{2,3} IgG antibodies are less helpful due to substantial variation between individuals while virus isolation by conventional cell culture is difficult and not clinically feasible. DNA hybridization and gene-amplification methods are reliable especially in diagnosing recurrent or persistent infection, since antibody production may be absent or minimal in such individuals.² Parvovirus B19 viral DNA in sera of symptomatic patients quantified by real-time PCR have also been found to correlate with clinical manifestations including erythema infectiosum and aplastic crisis.⁷

While patients with hematological or immunological diseases are known to suffer more severe disease after infection,⁸ the spectrum of disease manifestation is less well defined compared to previously healthy patients.^{2,4} The effects of viral load on clinical manifestations has not been well described previously. The aim of the retrospective case-series analysis is to present demographical, clinical, laboratory, and treatment features of parvovirus-infected patients by comparisons between patients with and without underlying diseases, and between patients with high and low viral loads.

Methods

Patients

Real-time PCR for parvovirus B19 was made available in the National Taiwan University Hospital and Children's Hospital, which is one of the largest referral center in Taiwan, since 2009. All patients whose serum tested positive for parvovirus B19 by real-time PCR from January 2009 to May 2018 were enrolled into this study. All patients were examined at least once by a pediatrician or internist during their clinical course. PCR for viral detection were ordered

after consultation with an infectious disease specialist. This study was approved by the Institutional Review Board.

Demographic and clinical data

The demographic and clinical data at time of parvovirus B19 infection diagnosis were collected retrospectively by the same investigator. A standardized form was used to extract data, including age, gender, underlying diseases (mainly focusing on immunosuppression, hematologic disorders and hemolytic anemia, and cardiopulmonary diseases), clinical manifestations, and treatment modalities. Patients were divided into two groups based on their clinical status: patients with underlying diseases, including immunologic (human immunodeficiency virus-(HIV) infection, solid-organ transplantations, and patients treated with immunosuppressive drugs), hematologic (hereditary anemia and thalassemia), cardiopulmonary (congenital heart disease and pulmonary hypertension); and immunocompetent patients with no history of hemolytic anemia, defined as previously healthy patients. Vital signs were compared with age-appropriate reference ranges.⁹ Duration of diagnosis was defined as time from symptom onset to the first positive PCR. Viral load quantification was available since 2011. High and low viral load was defined as viral load above and below the median respectively for patients with a qualified viral load.

Hematological data

Complete blood counts were obtained from the medical record system. Where available, a baseline cell count up to 2 months before diagnosis of parvovirus B19 infection were compared with counts at diagnosis. Hematological data were compared with age-appropriate reference ranges.⁹ Cytopenia were defined as cell counts below the reference range for age-specific population. Investigators cross-checked all patients with cytopenia to confirm absence of sepsis or septic shock defined by changes in Sequential Organ Failure Assessment (SOFA) score¹⁰ before enrollment.

Detection of parvovirus B19 by real-time PCR

Serum samples were subjected to DNA extraction using Roche MagNA Pure LC 2.0 (Roche Diagnostics GmbH, Mannheim, Germany). In-house primers specific for parvovirus B19 major (VP2) capsid protein generating a 172-bp fragment were designed based on established studies^{11,12}: forward primer, 5'-CCCAGAGCACCATTATAAGG-3'; and reverse primer, 5'-GTGCTGAACTCTAAAGGTGAA-3'. Amplification was performed with Roche LightCycler 1.5 using the following concentrations: 5 μ L of LightCycler RNA Amplification Kit SYBR Green I (TaKaRa), 4 μ L of template DNA, and 0.5 μ L of each primer. After an initial denaturation phase of one minute at 95 °C, 50 cycles of PCR amplification were performed at 94 °C for five seconds, 55 °C for 10 s, and 72 °C for 10 s. Positive and negative controls were used in every batch. Based on the mean threshold cycle for each dilution, a standard curve was

Table 1 Characteristics of patients with parvovirus B19 infection.

Characteristics	31 (100)
Sex	
Female	12 (39)
Male	19 (61)
Median age (years)	7.5 (0.0–80.8)
Season of illness onset	
Winter (December 1 to February 28)	6 (19)
Spring (March 1 to May 31)	7 (23)
Summer (June 1 to August 31)	7 (23)
Autumn (September 1 to November 30)	11 (35)
Underlying diseases	14 (45)
Immunologic	6 (19)
Human immunodeficiency virus carrier	2
Autoimmune hemolytic anemia	1
Autoimmune encephalitis	1
Transplant recipient	1
Juvenile myelomonocytic leukemia	1
Hematologic	5 (16)
Hereditary spherocytosis	3
Hemoglobin H disease	1
Thalassemia minor	1
Cardiopulmonary	3 (10)
Pulmonary hypertension	2
Transposition of great arteries	1
Clinical presentation ^e	
Fever	28 (90)
Skin rash	15 (48)
Fatigue	10 (32)
Pallor	6 (19)
Shock	5 (16)
Traceable sick contacts	9 (29)
Physical findings ^e	
Tachycardia	11 (36)
Tachypnea	9 (29)
Hepatosplenomegaly	8 (26)
Lymphadenopathy	6 (19)
Laboratory findings ^a	
Anemia	13 (42)
Leukopenia	12 (39)
Thrombocytopenia	14 (45)
Symptomatic duration prior to PCR diagnosis (days)	8.0 (0.0–95.0)
Median PCR viral load (copies/mL sera) ^b	5.5×10^5 (2.8×10^3 – 2.0×10^{13})
Initial impression prior to positive PCR	
Erythema infectiosum	7 (23)
Upper respiratory tract infection	5 (16)
Acute tonsillitis	4 (13)
Fever of unknown origin	4 (13)
Neutropenic fever	3 (10)

Table 1 (continued)

Characteristics	31 (100)
Mycoplasma pneumoniae infection	3 (10)
Measles infection	3 (10)
Others ^c	2 (6)
Hospitalized	17 (55)
Intensive care	5 (16.7)
Treatment administered ^e	
Packed red blood cells	12 (39)
Intravenous immunoglobulin	5 (16)
Hospital days for admitted patients (days) ^d	12.5 (3.0–88.0)
Complication	5 (16)
Mortality	1 (3)

^a Data available for 21 patients.

^b Data available for 22 patients.

^c Myocarditis (n = 1), and non-immune hydrops fetalis (n = 1).

^d Data for 16 patients.

^e Some patients had more than one presentation or physical finding, or received more than one treatment.

Data are presented as n (%), or median (range) unless otherwise specified.

PCR = polymerase chain reaction.

generated and the number of template molecules was calculated for each sample.

Statistical analysis

Data was analyzed using SPSS for Mac version 25 (SPSS Inc., Chicago, IL, USA). Biological and demographical data were compared by means of Fisher's exact test and Mann–Whitney U test where appropriate. A p value below 0.05 was considered statistically significant.

Results

Patient characteristics

In total, 31 patients (19 male/12 female) had real-time PCR-confirmed parvovirus B19 infection during 2009–2018 (Table 1). Thirteen patients were outpatients while 18 were inpatients with median hospitalization of 12.5 days. There were no age or seasonal peak incidences observed during the study period, although there is a trend of higher disease incidence during summer and autumn (Fig. 1). Fourteen (45%) patients had a preexisting comorbidity, including six (19%) with immunologic disease, five (16%) with hematologic disease, and three (10%) with cardiopulmonary disease. The classical presentation of erythema infectiosum - fever and skin rash, were found in 90% and 48% of all patients respectively. The median symptomatic duration prior to PCR diagnosis was eight days, with a range of zero (due to traceable sick contacts) and 95 days. The median serum viral load was 5.5×10^5 copies/mL.

Patients received a wide range of initial diagnosis prior to a positive parvovirus B19 PCR test. Erythema infectiosum

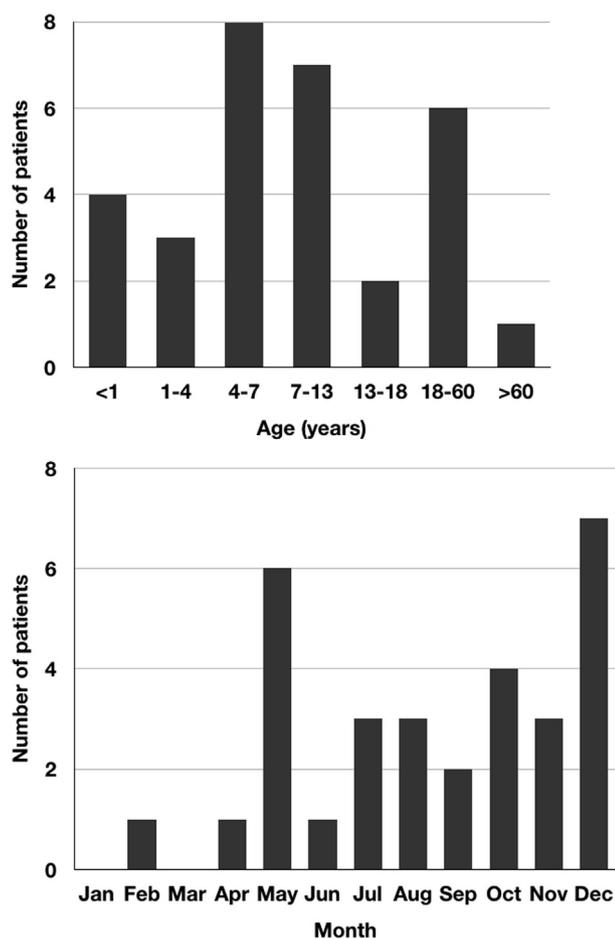


Figure 1. Age of patients and month of illness onset in patients infected with parvovirus B19.

was the initial diagnosis in only seven (23%) patients. There were a cluster of three cases whose initial impression was measles. Non-immune hydrops fetalis (NIHF) was diagnosed in a late preterm newborn with an otherwise unremarkable pregnancy who presented with sudden decrease in fetal movements and poor fetal heartbeats. A previously healthy 13-year old female who presented with chest pain and shock subsequently developed acute viral myocarditis. The only mortality in the series was a 3-month old female who died from intraabdominal bleeding due to severe coagulopathy after hepatic failure.

There was no difference between patients with early and late diagnosis in terms of age, proportion of patients with underlying disease, symptoms, laboratory findings, nor viral load.

Previously healthy patients vs patients with underlying diseases

There were no difference in gender, age, and symptomatic duration prior to diagnosis between previously healthy patients and patients with an underlying disease (Table 2). In previously healthy patients, a significantly higher proportion had a skin rash compared to patients with underlying disease, whom presented with higher proportion of fatigue

and pallor. Tachycardia and hepatosplenomegaly were significantly higher in patients with underlying disease compared to patients who were previously healthy, likely reflecting a higher proportion with anemia in patients with underlying diseases. Patients with underlying diseases had significantly higher parvovirus B19 viral load in the serum compared to previously healthy patients. Nevertheless, the maximum decline in hemoglobin nor number of cytopenia were not significant between the two groups.

Patients with hematologic diseases had a borderline higher proportion suffering from pancytopenia compared with previously healthy patients ($p = 0.050$). However, this was not observed in patients with immunologic diseases versus previously healthy patients.

On treatment modalities, packed red-cell transfusion was given to 71% of patients with underlying diseases and 12% of previously healthy patients. The median duration of hospitalization, proportion requiring intensive care, higher level of care at discharge, and death were not significantly different between the two groups.

Patients with high vs low viral loads

Twenty-two patients had a quantified viral load with median of 5.5×10^5 copies/mL sera. There was no difference in gender and symptomatic duration between patients with high and low viral loads (Table 3). However, patients with high viral loads were significantly older compared to patients with low viral loads. There was a trend toward previously healthy patients having a lower viral load ($p = 0.080$), and patients with immunologic comorbidity having a higher viral load ($p = 0.090$).

Although the maximum decline in hemoglobin, duration of hospitalization, and treatments were not significantly different between patients with high and low viral loads, a higher proportion of patients with high viral loads presented with fatigue, likely due to significantly higher proportion with anemia compared to patients with low viral loads.

Discussion

This nine-year retrospective case series documents the wide spectrum of parvovirus B19 infection in both previously healthy hosts and hosts with underlying diseases encompassing children and adults. Only 23% of patients with parvovirus B19 infection presented as typical erythema infectiosum. In our study, patients with underlying diseases were more likely to present with atypical symptoms, such as fatigue and pallor, rather than the classical presentation of erythema infectiosum. The erythematous rashes of parvovirus B19 infection, usually appearing 2 weeks after initial infection, are due to formation and deposition of immune complexes in the skin.^{2,15} Appearance of a rash may imply near resolution of viremia and predicts a self-limited course.⁴ In accordance with some earlier reports,⁸ our results suggest patients with underlying disease have limited ability in clearing the virus and recovery from disease.

Most patients who did not have classical signs or symptoms of parvovirus B19 infection were initially managed

Table 2 Comparison of characteristics between patients who are previously healthy and patients with underlying diseases.

Characteristics	Previously healthy	Underlying diseases	p-value
	17 (55)	14 (45)	
Male sex	11 (65)	8 (57)	NS
Age (years)	6.8 (0.8–40.9)	12.4 (0.0–80.8)	NS
Symptomatic duration prior to PCR diagnosis (days)	7.0 (0.0–16.0)	8.5 (4.0–95.0)	0.192
Clinical presentation ⁱ			
Fever	15 (88)	13 (93)	NS
Skin rash	14 (82)	1 (7)	< 0.001 ^g
Fatigue	2 (12)	8 (57)	0.018 ^g
Pallor	0 (0)	6 (43)	0.004 ^g
Shock	1 (6)	4 (29)	0.148
Physical findings ⁱ			
Tachycardia	3 (18)	8 (57)	0.031 ^g
Tachypnea	3 (18)	6 (43)	0.233
Hepatosplenomegaly	1 (6)	7 (50)	0.011 ^g
Lymphadenopathy	3 (18)	3 (21)	NS
Laboratory findings			
Anemia	2 (12) ^a	11 (79) ^b	0.056
Leukopenia	2 (12) ^a	10 (71) ^b	0.159
Thrombocytopenia	4 (23) ^a	10 (71) ^b	NS
Maximum decline in hemoglobin (g/dL)	2.0 (0.7–5.1) ^c	3.2 (0.4–7.0) ^d	NS
Number of cytopenia(s)	1.0 ^a (0.0–3.0)	2.5 ^b (0.0–3.0)	0.168
PCR viral load (copies/mL sera)	8.0 × 10 ⁴ (2.8 × 10 ³ - 8.8 × 10 ⁶) ^e	4.5 × 10 ⁸ (9.0 × 10 ³ - 2.0 × 10 ¹³) ^f	0.025 ^h
Treatment administered ⁱ			
Packed red blood cell transfusion	2 (12)	10 (71)	0.001 ^g
Intravenous immunoglobulin	3 (18)	2 (14)	NS
Hospitalized	4 (23)	13 (93)	< 0.001 ^g
Intensive care	1 (6)	4 (29)	0.148
Hospital stay (days)	18.5 (3.0–39.0)	11 (4.0–91.0)	NS
Higher level of care at discharge than at admission	2 (12)	3 (21)	NS
Death	0 (0)	1 (7)	NS

^a Data available for 7 patients.

^b Data available for 14 patients.

^c Data available for 4 patients.

^d Data available for 11 patients.

^e Data available for 13 patients.

^f Data available for 9 patients.

^g Indicates statistically significant by Fisher's exact test.

^h Indicates statistically significant by Mann–Whitney U test.

ⁱ Some patients had more than one presentation or finding, or received more than one treatment.

Data are presented as n (%), or median (range) unless otherwise specified.

NS = not significant.

WBC = white blood cell.

PCR = polymerase chain reaction.

under the impression of upper respiratory tract infection, fever of unknown origin, or neutropenic fever with supporting laboratory findings. Nevertheless, complications and mortality were infrequent even with a large proportion of patients with underlying diseases.

Infection of erythrocytes and their precursors by parvovirus B19 is a well-known phenomenon.^{1,2} Globoside (erythrocyte P antigen), a neutral glycolipid and acts as a cellular receptor, accounts for the tissue tropism of parvovirus B19.¹⁴ The nonstructural protein of parvovirus B19 is cytotoxic and responsible for the death of erythroid progenitors and via cell cycle arrest and apoptosis.^{2,17}

Typically, transient reticulocytopenia caused by parvovirus B19 infection does not lead to clinical anemia as a result of the long lifespan of erythrocytes in healthy adults (Fig. 2).¹⁶ In contrast, patients with increased destruction of or a high demand for erythrocytes, such as hemolytic anemia or hereditary spherocytosis, may suffer from transient aplastic crisis.¹⁷ Although the inhibition of the erythroid precursors is most pronounced, parvovirus affects other cell lineages as well.^{8,18} Hanada et al.¹⁹ demonstrated that incubation of a normal bone marrow with parvovirus-containing serum significantly inhibited erythroid (CFU-E), myeloid (CFU-GM), and megakaryocytic

Table 3 Comparison of characteristics between patients with viral loads above and below the median of 5.5×10^5 copies/mL sera.

Characteristics	Viral load		p-value
	< 5.5×10^5 copies/mL sera	> 5.5×10^5 copies/mL sera	
	11 (50)	11 (50)	
Male sex	7 (64)	7 (64)	NS
Age (years)	6.2 (0.8–12.5)	18.2 (3.3–80.8)	0.008^d
Symptomatic duration prior to PCR diagnosis (days)	7.0 (1.0–16.0)	9.0 (0.0–36.0)	NS
Previously healthy	9 (82)	4 (36)	0.080
Hematologic disease	0 (0)	3 (27)	0.214
Immunologic disease	0 (0)	4 (36)	0.090
Cardiopulmonary disease	2 (18)	0 (0)	NS
Symptoms ^e			
Fever	9 (82)	11 (100)	NS
Skin rash	8 (73)	3 (27)	0.086
Fatigue	1 (9)	7 (64)	0.024^c
Pallor	0 (0)	4 (36)	0.090
Shock	1 (9)	1 (9)	NS
Physical findings ^e			
Tachycardia	3 (27)	5 (45)	NS
Tachypnea	3 (27)	3 (27)	NS
Hepatosplenomegaly	1 (9)	4 (36)	NS
Lymphadenopathy	3 (27)	2 (18)	NS
Laboratory findings			
Anemia	1 (9) ^a	7 (64) ^b	0.010^c
Leukopenia	3 (27) ^a	5 (45) ^b	NS
Thrombocytopenia	4 (36) ^a	6 (55) ^b	NS
Maximum decline in hemoglobin (g/dL)	2.1 (0.1–3.4) ^a	2.9 (0.4–5.3) ^b	NS
Treatment administered ^e			
Packed red blood cell	1 (9)	6 (55)	0.063
Intravenous immunoglobulin	2 (18)	2 (18)	NS
Hospitalized	4 (36)	7 (64)	NS
Clinical course (days)	18.0 (12.0–21.0)	8.5 (6.0–39.0)	NS

^a Data available for 7 patients.

^b Data available for 8 patients.

^c Indicates statistically significant by Fisher's exact test.

^d Indicates statistically significant by Mann–Whitney U test.

^e Some patients had more than one presentation or finding, or received more than one treatment.

Data are presented as n (%), or median (range) unless otherwise specified.

NS = not significant; PCR = polymerase chain reaction.

(CFU-Mgk) growth. The presence of globoside on tissues other than erythroid precursors, such as hepatocytes,¹⁵ megakaryocytic, endothelium, and myocardium²⁰ underlies the diverse clinical presentation of parvovirus B19 infection. Up to 59% of children with chronic hemolytic anemia developed pancytopenia during parvovirus infection in a series reported by Cauff et al.²¹ In our series, a higher proportion of patients with underlying diseases and patients with high viral loads suffer from anemia. An earlier study also found that bicytopenia and pancytopenia were more frequently seen in immunocompromised patients.⁸ Patients with hematologic disease had a borderline higher proportion of developing pancytopenia, but no similar tendency was found among patients with immunologic disease compared to previously healthy patients. Parvovirus-induced pancytopenia may be multifactorial. In addition to a direct cytopathic effect, parvovirus has been shown to recruit CD8⁺ T cells causing increased secretion

of IFN- γ and TNF- α leading to hypersplenism and hemophagocytosis.^{22,23} Two of our cohort suffered from secondary hemophagocytic lymphohistiocytosis, which is well reported in literature.

Our data shows patients with underlying diseases had a higher viral load compared to previously healthy patients. Patients with a higher than median viral load of 5.5×10^5 copies/mL sera were older; A higher proportion of them suffered from fatigue likely due to anemia compared to patients with a low viral load. We found no literature describing the association of older age with a higher parvovirus B19 viral load.

Two patients in our series were patients living with HIV. Pure red-cell aplasia may be the first manifestation of infection with HIV.² In fact, prior to highly active antiretroviral therapy, persistent parvovirus B19 infection was a leading diagnosis among HIV-positive men with anemia.²⁴ In a cross-sectional study in Taiwan, the seroprevalence for

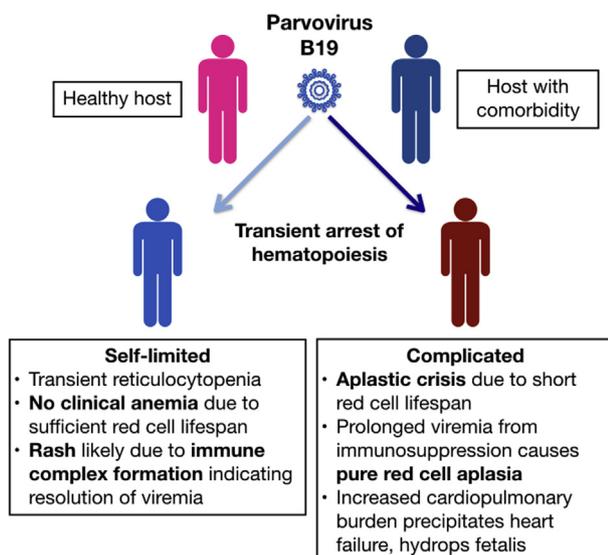


Figure 2. A healthy host who is infected with parvovirus B19 will suffer transient reticulocytopenia but no clinical anemia as erythrocyte lifespan is sufficient to bridge the transient arrest of hematopoiesis. On the contrary, hosts with hematologic diseases will suffer aplastic crisis due to relatively short erythrocyte lifespan; while hosts with immunologic diseases will suffer pure red cell aplasia due to delayed viral clearance. As a result, they are more likely to require transfusions due to cytopenia, or suffer cardiopulmonary failure due to the increased circulatory stresses.

parvovirus B19 between HIV-positive and HIV-negative men who have sex with men were similar.²⁵ Notably, parvovirus B19 seroprevalence was significantly higher in injection drug users (OR = 6.74), regardless of HIV status,²⁵ highlighting blood-borne transmission as an alternative route of infection and increased vigilance needed when encountering such patients.

The differential diagnosis of erythema infectiosum includes other viral exanthems including measles and dengue.^{26,27} Interestingly, three patients in our cohort were initially misdiagnosed as measles from a single positive IgM test. Parvovirus B19 infection has been implicated in false-positive IgM assays for measles,²⁶ EBV, herpes simplex virus, and HHV6 viral infections.²⁸ Cross-reactive antibodies, polyclonal B cell activation, and a vigorous immune response were implicated as mechanisms for false-positive IgM tests. To improve diagnostic accuracy, IgM positivity should be followed up using serial samples to determine if levels are rising, class capture IgM, testing for pathogen PCR, or documenting seroconversion of IgG.²⁹ Hence, in Taiwan where measles is non-endemic, and a high measles vaccine coverage rate, relying on a single IgM test would be risky as positive predictive value declines with falling disease prevalence.²⁸ Our patients subsequently tested negative for measles and positive for parvovirus B19 via PCR. The experiences gained from this cohort were that IgM detection is not acceptable as a standalone test and thorough investigations are still warranted when vaccinated patients with viral exanthemata test positive for measles IgM in a non-endemic setting.

Fetuses acquire parvovirus B19 via transplacental transmission.² Infection during the second trimester poses the greatest risk of NIHF due to the increased demand of hematopoiesis in the fetal liver, increase in red cell mass, and a reduction in red cell life span.³⁰ Highest risk of infection occurs during epidemics and is correlated with number of children at home.³¹ Although most infected fetuses have spontaneous resolution with no adverse outcomes,³² possible effects on the brain and neurodevelopment outcomes remains to be elucidated.¹³ PCR of amniotic fluid should be performed as part of the evaluation for hydrops fetalis besides maternal IgG and IgM for parvovirus B19.^{13,31} As Taiwanese patients were reported to have low seroprevalence toward parvovirus B19,⁶ there could be potential epidemics regionally in the future. Poor awareness of the disease among obstetricians might explain low case number in our series as most first- and second-trimester spontaneous abortions secondary to parvovirus B19 infection might be underdiagnosed.

Most cases of parvovirus infection in children do not require isolation nor specific therapy. Supportive care including fluid replacement and transfusion may be necessary for patients with symptomatic anemia.³³ For immunosuppressed patients, discontinuing steroids or immunosuppressive therapy, or by instituting antiretroviral therapy in patients with AIDS, may terminate pure red-cell aplasia and persistent viral infection.² Intravenous immunoglobulin (IVIg) are a good source of antibodies against parvovirus B19. A 5-day course of IVIg at 0.4 g per kilogram body weight induces an increase in reticulocyte count, hemoglobin level, and a prompt decline in viral load.² Intrauterine erythrocyte transfusions have been shown to reduce fetal mortality in NIHF.³²

While subclinical viremia in patients does not necessarily imply that viral replication is ongoing,³⁴ all our cases were tested whilst symptomatic. Virology PCR was ordered after consultation with an infectious disease specialist. Hence, the risk of a false positive result should be low. Prolonged viral shedding in immunocompromised patients was also a concern, but the addition of serum IgM, which is unavailable in our institution, offered limited benefit since antibody production would be limited in such populations.^{2,4} The major weakness of the current study is the small sample size. Despite using a highly sensitive method, we found only 31 patients over a span of nine years. We believe most erythema infectiosum were diagnosed based on clinical symptoms alone; while complicated cases might have been missed or underreported due to limited clinical understanding. As the sample size is admittedly small, we did not further classify patients by their respective underlying diseases. Viral load may vary markedly between hosts and is dependent on duration of symptom onset and diagnosis. As with retrospective studies, we have no control of host factors, duration between symptom onset to laboratory evaluation and viral load determination. These factors contributed to the heterogeneous cohort and findings such as the association between patients with older age having a higher viral load. Nevertheless, we were able to document important signs and symptoms in patients with underlying diseases who were viremic, highlighting the polymorphic presentations of parvovirus infection in such hosts and need for increased clinical vigilance. .

In summary, we presented a comprehensive series of parvovirus B19 infections highlighting the nonspecific and atypical presentations in patients with comorbidity. An extended awareness on the multifaceted presentation and actual pathogenic role of parvovirus B19 will continue to improve our efforts in diagnostic, therapeutic, and prophylactic options in future.

Conflicts of interest

All authors have no conflict of interest to declare in relation to this article.

References

- Servant-Delmas A, Lefrere JJ, Morinet F, Pillet S. Advances in human B19 erythrovirus biology. *J Virol* 2010;**84**:9658–65.
- Young NS, Brown KE. Parvovirus B19. *N Engl J Med*. 2004;**350**:586–97.
- Makhlouf MM, Elwakil SG, Ibrahim NS. Molecular and serological assessment of parvovirus B-19 infection in Egyptian children with sickle cell disease. *J Microbiol Immunol Infect* 2017;**50**:565–9.
- Rogo LD, Mokhtari-Azad T, Kabir MH, Rezaei F. Human parvovirus B19: a review. *Acta Virol* 2014;**58**:199–213.
- Mossong J, Hens N, Friederichs V, Davidkin I, Broman M, Litwinka B, et al. Parvovirus B19 infection in five European countries: seroepidemiology, force of infection and maternal risk of infection. *Epidemiol Infect* 2008;**136**:1059–68.
- Lin K-H, You S-L, Chen C-J, Wang C-F, Yang C-S, Yamazaki S. Seroepidemiology of human parvovirus B19 in Taiwan. *J Med Virol* 1999;**57**:169–73.
- Ishikawa A, Yoto Y, Tsugawa T, Tsutsumi H. Quantitation of human parvovirus B19 DNA in erythema infectiosum and aplastic crisis. *J Med Virol* 2014;**86**:2102–6.
- Wolfrohm A, Rodriguez C, Michel M, Habibi A, Audard V, Benayoun E, et al. Spectrum of adult Parvovirus B19 infection according to the underlying predisposing condition and proposals for clinical practice. *Br J Haematol* 2015;**170**:192–9.
- Fleming S, Thompson M, Stevens R, Heneghan C, Plüddemann A, Maconochie I, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. *The Lancet* 2011;**377**:1011–8.
- Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). *JAMA* 2016;**315**:801–10.
- Koch WC, Adler SP. Detection of human parvovirus B19 DNA by using the polymerase chain reaction. *J Clin Microbiol* 1990;**28**:65–9.
- Erdman DD, Durigon EL, Wang Q-Y, Anderson LJ. Genetic diversity of human parvovirus B19: sequence analysis of the VP1/VP2 gene from multiple isolates. *J Gen Virol* 1996;**77**:2767–74.
- Ornoy A, Ergaz Z. Parvovirus B19 infection during pregnancy and risks to the fetus. *Birth Defects Res* 2017;**109**:311–23.
- Brown KE, Anderson SM, Young NS. Erythrocyte P antigen: cellular receptor for B19 parvovirus. *Science* 1993;**262**:114–7.
- Kerr JR. A review of blood diseases and cytopenias associated with human parvovirus B19 infection. *Rev Med Virol* 2015;**25**:224–40.
- Smith-Whitley K, Zhao H, Hodinka RL, Kwiatkowski J, Cecil R, Cecil T, et al. Epidemiology of human parvovirus B19 in children with sickle cell disease. *Blood* 2004;**103**:422–7.
- Lee Y-M, Tsai W-H, You J-Y, Ing-Tiau Kuo B, Liao P-T, Ho C-K, et al. Parvovirus B19 infection in Taiwanese patients with hematological disorders. *J Med Virol* 2003;**71**:605–9.
- Servant-Delmas A, Morinet F. Update of the human parvovirus B19 biology. *Transfus Clin Biol* 2016;**23**:5–12.
- Hananda T, Koike K, Takeya T, Nagasawa T, Matsunaga Y, Takita H. Human parvovirus B19-induced transient pancytopenia in a child with hereditary spherocytosis. *Br J Haematol* 1988;**70**:113–5.
- Furukawa M, Kaji K, Masuda H, Ozaki K, Asada S, Koizumi A, et al. Severe aplastic anemia following parvovirus B19-associated acute hepatitis. *Case Reports Hepatol* 2017;**2017**:1359486.
- Cauff BE, Quinn CT. Transient parvovirus-associated hypoplasia of multiple peripheral blood cell lines in children with chronic hemolytic anemia. *Pediatr Blood Canc* 2008;**50**:861–4.
- Papadogiannakis NTT, Fischler B, Norbeck O, Broliden K. Active, fulminant, lethal myocarditis associated with parvovirus B19 infection in an infant. *Clin Infect Dis* 2002;**35**:1027–31.
- Yuan C, Asad-Ur-Rahman F, Abusaada K. A rare case of hemophagocytic lymphohistiocytosis associated with parvovirus B19 infection. *Cureus* 2016;**8**:e897.
- Abkowitz JL, Brown KE, Wood RW, Kovach NL, Green SW, Young NS. Clinical relevance of parvovirus B19 as a cause of anemia in patients with human immunodeficiency virus infection. *J Infect Dis* 1997;**176**:269–73.
- Lee Y-M, Chuang S-Y, Wang S-F, Lin Y-T, Chen Y-M. Epidemiology of human herpesvirus type 8 and parvovirus B19 infections and their association with HIV-1 among men who have sex with men and injection drug users in Taiwan. *J Microbiol Immunol Infect* 2014;**47**:233–8.
- Ciccone FH, Carvalhanas TR, Afonso AM, Flannery B, Waldman EA. Investigation of measles IgM-seropositive cases of febrile rash illnesses in the absence of documented measles virus transmission, State of São Paulo, Brazil, 2000-2004. *Rev Soc Bras Med Trop* 2010;**43**:234–9.
- Chen C-H, Huang Y-C, Kuo K-C, Li C-C. Clinical features and dynamic ordinary laboratory tests differentiating dengue fever from other febrile illnesses in children. *J Microbiol Immunol Infect* 2018;**51**:614–20.
- Woods CR. False-positive results for immunoglobulin M serologic results: explanations and examples. *J Pediatric Infect Dis Soc* 2013;**2**:87–90.
- Landry ML. Immunoglobulin M for acute infection: true or false? *Clin Vaccine Immunol* 2016;**23**:540–5.
- Lamont RF, Sobel JD, Vaisbuch E, Kusanovic JP, Mazaki-Tovi S, Kim SK, et al. Parvovirus B19 infection in human pregnancy. *BJOG* 2011;**118**:175–86.
- Valeur-Jensen AK, Pedersen CB, Westergaard T, Jensen IP, Lebech M, Andersen PK, et al. Risk factors for parvovirus B19 infection in pregnancy. *JAMA* 1999;**281**:1099–105.
- Crane J, Mundle W, Boucoiran I, Gagnon R, Bujold E, Basso M, et al. Parvovirus B19 infection in pregnancy. *J Obstet Gynaecol Can* 2014;**36**:1107–16.
- Broliden K, Tolfvenstam T, Norbeck O. Clinical aspects of parvovirus B19 infection. *J Intern Med* 2006;**260**:285–304.
- Molenaar-de Backer MW, Russcher A, Kroes AC, Koppelman MH, Lanfermeijer M, Zaaier HL. Detection of parvovirus B19 DNA in blood: viruses or DNA remnants? *J Clin Virol* 2016;**84**:19–23.