Hematologic manifestations of Parvovirus B 19 infection

Ghada Algwaiz
Department of Medicine, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia, ghada_fahad@live.com

Abrar Alharbi
Department of Medicine, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

Khuloud Alsehaim
Department of Medicine, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

Ali Alahmari
Oncology Center, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

Riad El Fakih
Oncology Center, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

See next page for additional authors

Follow this and additional works at: https://www.hosct.org/hematology-oncology-and-stem-cell-therapy

Part of the Cancer Biology Commons, Hematology Commons, and the Oncology Commons

Recommended Citation
Algwaiz, Ghada; Alharbi, Abrar; Alsehaim, Khuloud; Alahmari, Ali; Fakih, Riad El; and Aljurf, Mahmoud (2022) “Hematologic manifestations of Parvovirus B 19 infection,” Hematology/Oncology and Stem Cell Therapy. Vol. 16 : Iss. 4 , Article 3.
Available at: https://doi.org/10.56875/2589-0646.1031

This Review Article is brought to you for free and open access by Hematology/Oncology and Stem Cell Therapy. It has been accepted for inclusion in Hematology/Oncology and Stem Cell Therapy by an authorized editor of Hematology/Oncology and Stem Cell Therapy.
Hematologic manifestations of Parvovirus B 19 infection

Authors
Ghada Algwaiz, Abrar Alharbi, Khuloud Alsehaim, Ali Alahmari, Riad El Fakih, and Mahmoud Aljurif
Hematologic Manifestations of Parvovirus B19 Infection

Ghada Algwaiz, Abrar Alharbi, Khuloud Alsehaim, Ali Alahmari, Riad El Fakih, Mahmoud Aljurfi

**Abstract**

Parvovirus B19 virus infection is widespread among humans because of its highly infectious and obstinate nature, with up to 80% of the population testing positive for IgG antibodies against the virus. Pronormoblasts observed in biopsy are the hallmarks of PVB19 infection. In addition, PVB19 affects the skin, heart, brain, joints, and liver and can be diagnosed through antibody detection or DNA detection via PCR. Due to its capsid proteins’ high affinity for bone marrow receptors, its main presentation is the suppression of bone marrow functions. It has been shown to affect patients with hemolytic anemia and patients with hematological malignancies, presenting with pure red cell aplasia. The main available effective treatment option is IV immunoglobulins; however, the risk of recurrence remains high after treatment.

**Keywords:** Parvovirus B19, Bone marrow, Infection, Pure red cell aplasia

1. Introduction

Parvovirus B19 (PVB19), the only Parvovirdae virion pathogenic to humans, was first discovered in 1975 in the serum samples of normal blood bank donors, while screening for hepatitis B virus [1]. The first report of human infection was in 1981. Currently, 50–80% percent of the human population is infected during childhood, while the percentage of positive anti-parvovirus IgG antibodies in adult populations are reaching 70% [2,3]. Having measurable serum IgG antibodies denotes previous exposure and lifelong immunity to the virus [4,5]. In addition to humoral immunity, cell mediated viral immunity has also been demonstrated [6,7].

The icosahedral virion of PVB19 contains 60 copies of the capsid proteins, VP1 and VP2 (95% of the virion), which encloses a non-enveloped, linear, 22–26 nm single stranded DNA [8]. VP1 is the primary target for antibodies and plays a role in initiation of infection and chronic inflammation, playing an important role in the pathogenesis of PVB19 infection [9]. The protein responsible for PVB19 replication is nonstructural 1 (NS1), which trans-regulates, among other promoters, the viral P6 promoter and leads to erythroid cell precursor cytolysis via caspase 3 [10,11].

In humans, PVB19 binds to a glycolipid receptor called P antigen or globoside (Gb4). Cellular and tissue tropism is based on the distribution of this receptor, and since it is highly expressed by the bone marrow erythroid lineage cells, it frequently leads to hematologic problems. Individuals who lack P antigen genetically have a natural immunity to PVB19 infection [12]. Other cell types that do express P antigen (such as in kidneys, liver, and platelets) are not a target of infection, but are still susceptible to infection, implicating another receptor, a-5 b1 integrin, in pathogenesis [13]. Once inside the cell, PVB19 induces cell cycle arrest, leading to cell lysis by dysregulation of the E2F family of transcription factors [14]. While there is no evidence of PVB19-DNA integration into human DNA, other viruses from the same family do integrate into...
human DNA, such as Mice Minute Virus (MMV) [15].

The absence of a lipid envelope and the limited DNA content make PVB19 extremely stable to physical inactivation and resistant to various offending agents, and as a result, can remain infectious under different conditions [16]. It can remain infectious up to 80 °C for 72 h, as well as in lipid solvents, and can only be inactivated by formalin, γ-irradiation and oxidizing agents [17]. PVB19 spreads via respiratory droplets, and from the nasopharyngeal area, it disseminates to the blood and other organs [16].

PVB19 is known to cause the pathognomonic erythema infectiosum, hydrops fetalis, arthralgia and hepatitis. However, due to the high viral tropism for the human bone marrow, hematological manifestation, with a wide variation in the clinical presentation, has been observed, depending on the immunologic status of the patient [18]. We herein, review the different characteristics of parvovirus infection, and its hematological manifestation, in addition to its diagnosis and treatment.

1.1. Pathology

Two percent of healthy individuals can have PVB19-DNA in the bone marrow (BM) [19]. Besides the BM, PVB19 has been detected in other organs, including, but not limited to, the skin, liver, and kidney. In the skin, in addition to viral genome, biopsies show interstitial histiocytic infiltrates, fragmentation of collagen and mononuclear cellular vascular injury patterns. Other features include mesenchymal mucinosis and papillary dermal edema. Some findings suggest a delayed-type hypersensitivity reaction [20]. In the kidney biopsies, diffuse endocapillary cellular infiltration is present, with tuft collapse and vacuolation ofglomerular epithelial cells. A starry sky pattern appears on immunofluorescence, due to dense granular C3 deposition [21]. In liver biopsies, apart from PVB19 DNA and a picture of acute lobular hepatitis, no remarkable histopathological findings have been reported [22,23].

Peripheral blood smear typically shows normal megalakocytes and granulocytes, however, different RBC abnormalities can also be seen (anisocytosis, poikilocytosis, nucleated RBC, etc.) [24]. Microscopic examination of the BM shows several abnormalities, mainly affecting the different stages of red cell maturation, resulting in maturation arrest and accumulation of early RBC precursors. The typical findings are the presence of giant pronormoblasts, also known as Lantern cells, with no further maturation beyond this stage [25]. These pronormoblasts were originally described in 1948, by Owren, as large erythroid precursors with vacuolated cytoplasm and eosinophilic nuclear inclusions. Along with this, erythroid hypoplasia is frequently seen [3,26–28]. Occasionally, hemopagocytosis may also be present [29].

On electron microscopy of the BM, randomly distributed intranuclear particles, displacement of the nuclear chromatin by viral particles, and cytoplasmic intravacuolar particles can be seen throughout the maturational spectrum of RBCs [30–32].

1.2. Diagnosis

To diagnose PVB19, either detecting viral antigen or viral antibody is vital [33,34]. Electron microscopy, B19 antigen enzyme-linked immunosorbent assays or hemagglutination could be used to isolate viral DNA [35]. However, the preferred and the most sensitive method is direct hybridization by polymerase chain reaction (PCR), especially in immunocompromised patients, where the antibody response is not optimal or is blunted [24,36]. Detection of IgM indicates acute infection and is found in 85% of patients with erythema infectiosum or aplastic crisis. IgM antibodies persist for 2–3 months from the time of infection [35]. Bone marrow biopsy, with demonstration of RBC maturation arrest, may be needed in cases with high clinical suspicion [8,9]. Detection of viral DNA and antibodies has been reported in a number of tissues (e.g. cerebrospinal fluid, synovial membranes), but their significance is unclear [27].

1.3. Transmission

In the first years after Parvovirus discovery, healthy individuals were inoculated with the live form of the virus through intranasal methods. After 1 week, they were found to have viremia, in addition to the presence of the virus in respiratory tract sections. No viral DNA was detected in the urine or feces. These findings suggest that the virus is transmitted through respiratory droplets [37]. On the other hand, anti-B19 IgG antibodies were also detected in blood and blood components of infected donors, which indicate another way of transmission, supported by identifying several cases in multi transfusion-dependent patients, like in thalassemia [38,39]. Blood transfusion transmission was considered one of most common causes of infection transmission in cancer and immunocompromised patients [40,41]. Plasma-derived factors, specifically
anti-hemophilic factor products, like factor VIII, were also reported to be a cause of transmission, due to the high virulence of PVB19, and its resistance to inactivation methods [42,43]. Moreover, parvovirus was also seen to be transmitted vertically from mother to fetus [44]. Although PVB19 infection is traditionally transmitted through respiratory droplets, blood transfusion is considered one of the most common causes of infection transmission in cancer and immunocompromised patients [67,68].

1.4. Spectrum of hematological manifestations

Pure Red Cell Aplasia (PRCA) is a rare hematological condition, with hypoplasia of the bone marrow and normal megakaryocytic and myeloid lineages, manifesting clinically as isolated normocytic normochromic anemia, with reticulocytopenia, in the absence of hemorrhage [45]. There is a congenital form, an acquired form and a viral-induced form, both of which are secondary to genetic defects. The known causes for acquired PRCA include immunologic causes, such as systemic lupus erythematosus, thymoma, rheumatoid arthritis and hematologic malignancies, most notably, myelodysplasia [16], early manifestation of aplastic anemia or other forms of bone marrow failure.

PRCA is the dominant manifestation of chronic parvovirus infection [12], which can be terminated by initiating therapy or stopping immunosuppressive therapy in immunosuppressed patients. PVB19 associated PRCA can be the first manifestation of infection in HIV [17]. For diagnosis, immunoglobulins against VP1/VP2 are tested, and viral DNA is detected via PCR. Testing against NS1 antibodies, which are detectable after 6 weeks of infection, is also done [46]. Traditionally, bone marrow evaluation is not needed routinely in suspected PVB19 related PRCA [47].

As mentioned before, given the high level of PVB19 receptors in the bone marrow, hematologic manifestations are frequently seen in the course of this infection. Typically, as the infection affects the early precursors in the bone marrow (especially RBC precursors), progressive decline in the production of the affected cells is observed until an immune response is elicited to clear the virus and restore marrow function. The duration and intensity of the decline depends on the half-life of the affected precursors, the bone marrow reserves, the immune status of the affected patient, and the presence of other hematologic diseases. In immunocompetent hosts with no marrow disorders, an immune response is elicited 10–14 days after infection, and subsequently, the marrow function is restored, resulting in a short self-limited illness. Patients who are unable to mount an immune reaction (e.g., patients with human immunodeficiency virus), or patients with underlying hematologic disorders (e.g., patients with hemolysis) will not have the same course. Prolonged infection or significant marrow dysfunction can happen in these patients, leading to delayed marrow recovery and its consequences [48–51].

1.5. In hemolytic anemias

Erythroid precursor ablation is an early event in the PVB19 infection course, resulting in reticulocytopenia, and subsequently, a non-productive, isolated normocytic, normochromic anemia [5]. If the PVB19 infection persists, then continuous ablation of the RBC precursors becomes chronic and results in pure red cell aplasia (PRCA). Therefore, PRCA can be a frequent complication of PVB19 infection in immunocompromised patients that cannot clear the infection quickly [28,52]. PVB19-associated PRCA can be the first manifestation of infection in HIV infected patients [16]. It is important to differentiate PVB19-associated PRCA from other causes of PRCA (congenital, secondary, etc.) as the management is different for each cause [28,50,52–54]. PVB19 infection can also affect other hematopoietic precursor cells by the same mechanism, and subsequently, may lead to thrombocytopenia or leukopenia [55].

The shorter half-life of RBCs in patients with hemolytic anemias makes them susceptible for transient PRCA after PVB19 infection, before immune clearance occurs [10,28,50,53,54]. Patients with chronic hemolysis may be at higher risk for PVB19 infection, because of frequent transfusion. The first time PVB19 was linked to clinical disease was in sickle cell disease (SCD). SCD patients are highly susceptible to PVB19 infection [56]. In a metanalysis on the seroprevalence, nearly half of SCD patients tested positive for IgG and/or IgM, which was especially high in poor and underdeveloped areas, and directly correlated with increased age, with no gender difference in homozygous SCD [55]. This could be due to multiple factors, including tropism to red blood precursor cells, frequent blood transfusions and lack of preventive vaccine. PVB19 can induce severe disease in this population, precipitating prolonged vaso-occlusive crisis, leading to splenic sequestration, glomerulonephritis, myocarditis and bone marrow embolism [57]. There is also an approximate 58 times greater risk of cerebrovascular episode in the 5-week period post a PVB19 infection [58].

Similar to SCD, the seroprevalence of PVB19 in thalassemia patients may be a little higher when
compared to the general population, because of the frequent blood transfusions in this group of patients [15,59,60]. In addition to PRCA, heart failure and encephalopathy have been reported in thalassemia patients after PVB19 infection [6,7,61–64]. Hereditary spherocytosis, as well as other chronic hemolytic states, share post PVB19 infection similarities with SCD and thalassemia patients [9,16,47].

1.6. In hematological malignancy and BMT

The prevalence of PVB19 infection in adults with hematological cancer and bone marrow transplants (BMT) is reported in a limited number of studies. It was published to range between 4 and 72%, with the highest percentage belonging to hematological malignancies [65–67]. Studies in the pediatric population show an increase in prevalence of infection in young adults, compared to children [35,68,69].

The exact prevalence of PVB19 infection in patients with hematologic malignancies is not available, but possibly mirrors that of the general population, or higher, because of the frequent blood transfusions in this population, combined with an immunosuppressed state [70]. The most common presentation is PRCA, which can be confused with a relapse of the primary disease as the two presentations share similar symptoms including fever, fatigue, pallor, arthralgia leukopenia, thrombocytopenia and pancytopenia [71–73].

A rarer presentation is an erythematous rash, which appears two weeks after infection, due to the lack of delayed antibody response and an inability to neutralize the infection, leading to a prolonged disease course with persistent viremia [71,72]. In 2019, a significant difference was reported between the viral load in patients with hematological malignancy and that in immunocompetent individuals, with the viral load in the former being higher than the latter [67]. However, the elevation of viral load in immunocompromised patients did not affect the drop in hemoglobin, hospital stay or treatment [74].

1.7. In immunocompetence

Although mostly asymptomatic, PVB19 infection in immunocompetent patients may present with idiopathic thrombocytopenia purpura (ITP). ITP is characterized by an acute onset of thrombocytopenia, with a history of viral infection. PVB19 could be the precipitating factor for thrombocytopenia via two mechanisms: central and peripheral. Central thrombocytopenia is related to bone marrow suppression by PVB19, through the NS1 protein, which inhibits the megakaryocytic colony formation. While the peripheral (or destructive) thrombocytopenia is an immunological phenomenon that is explained by antiplatelet antibodies, leading to platelet sequestration in the reticuloendothelial organs [75–78].

1.8. Extra-hematological manifestations

PVB19 infection in the healthy individual could be asymptomatic or associated with non-specific symptoms, similar to common flu presentation [6]. In cases of erythema infectosum, the flu-like presentation may be followed, two weeks later, with facial erythema, a pathognomonic “slapped-cheeks” appearance. Shortly after this, a maculopapular rash appears all over the body, with a predominance on sun-exposed areas [17]. Arthropathy is seen in 30–60% of infected adults, with a presentation similar to rheumatoid arthritis. Pattern of involved joints may be either symmetrical or asymmetrical arthralgia in both small and large joints [79]. Neurological manifestations, in the form of encephalopathy, meningitis and neuropathy with regional complex pain syndromes, have been described with this infection [80–82]. Myocarditis, pericarditis and hepatitis are rare complications of PVB19 infection [83,84]. As viral receptors are also present on the placental cells, infection during pregnancy can lead to dramatic fetal complications. Anemia, hydrops fetalis, liver injury, myocarditis with heart failure and stillbirth can occur, especially if the infection happens during the first trimester of pregnancy, where the organogenesis happens [85–87]. (Table 1).

Table 1. Non-hematological manifestations of PVB19 Infection.

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Manifestation of PVB19 Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dermatological</td>
<td>Erythema (slapped cheek syndrome)</td>
</tr>
<tr>
<td></td>
<td>Maculopapular rash on sun-exposed areas</td>
</tr>
<tr>
<td></td>
<td>Reticulated truncal erythema</td>
</tr>
<tr>
<td></td>
<td>Acral petechiae</td>
</tr>
<tr>
<td></td>
<td>Lupus erythematosus or dermatomyositis-like rashes</td>
</tr>
<tr>
<td>Rheumatological</td>
<td>Arthropathy</td>
</tr>
<tr>
<td>Neurological</td>
<td>Encephalopathy</td>
</tr>
<tr>
<td></td>
<td>Meningitis</td>
</tr>
<tr>
<td></td>
<td>Neuropathy</td>
</tr>
<tr>
<td></td>
<td>Regional Complex Pain Syndrome</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Myocarditis</td>
</tr>
<tr>
<td></td>
<td>Pericarditis</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Hepatitis</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
</tr>
<tr>
<td>Reproductive</td>
<td>Hydrops Fetalis</td>
</tr>
<tr>
<td></td>
<td>Stillbirth</td>
</tr>
<tr>
<td>Others</td>
<td>Fever and chills</td>
</tr>
<tr>
<td></td>
<td>Sleeping disturbance</td>
</tr>
<tr>
<td></td>
<td>Malaise</td>
</tr>
<tr>
<td></td>
<td>Body pain</td>
</tr>
</tbody>
</table>
1.9. Treatment

Most patients with PVB19 will recover spontaneously without complications and will possibly go unnoticed. Currently, there is no approved antiviral agents or vaccines for PVB19. The obstacles facing the vaccine development include the lack of a cost-effective, standardized PVB19 neutralization essay. In patients who develop a complicated course of infection, intravenous immunoglobulin (IVIG) is the most frequently used treatment modality. As the infection is prevalent in the general population, it is expected that IVIG will carry significant neutralization of anti-PVB19 IgG antibodies, and this explains its efficacy [62].

In immunocompromised patients with PRCA, IVIG treatment corrected the hemoglobin level and caused a marked rise in reticulocyte count after the first course. Although the antibodies should provide protection against infection, 34% of patients relapse, with a mean time to relapses of 4.3 months [63]. Immunotherapy with PVB19-directed human monoclonal antibodies have been suggested as treatment for chronically infected patients [64].

IVIG can be administered safely with chemotherapy agents, making it an attractive choice. Conversely, rituximab and other anti-CD20 depleting agents, used in hematological malignancy protocols, have been shown to reactivate PVB19, resulting in chronic progressive neutropenia or cytopenia, and acute hepatitis [88–90]. Foscarnet has been proposed as an alternative to IVIG, due to its lower cost and it has observed to be non-inferior to IVIG in a trial on a kidney transplant patient with PVB19 infection [91].

Blood transfusion may be required in some cases, such as spleen sequestration or patients with hemodynamic instability [56]. Isolation of these patients is recommended during admission, to decrease the risk of contagion spread [70]. Lastly, no significant data on the effect of PVB19 on CAR-T cell therapy recipients have been reported. However, the persistent neutropenia, which is secondary to cytokine storm (CRS), in CAR-T cell therapy have been suggested to be due to an underlying PVB19 infection [92].

2. Conclusions

PVB19 is the only Parvoviridae virion pathogenic to humans. It has no envelope and has limited DNA content. The virus is prevalent among the general population and poses a higher risk for hematologic patients. PRCA is a unique manifestation in hematology and immunocompromised patients. A high degree of suspicion, depending on local epidemiology, is required to think about this infection in the appropriate settings. IVIG is an effective therapy and should be tried in most cases.

Conflict of interest

The authors declare that there are no conflicts of interest.

Acknowledgments

GA, AA wrote the first draft. RE, MA revised the first draft. All the co-authors revised and approved the final manuscript.

References

parvovirus B19 among patients with sickle cell disease. Bio-
[59] Lundqvist A, Tolfvenstam T, Brytting M, Stolt CM, Obeid KM. Infections with DNA viruses, adenovirus, poly-
[60] Kochethu G, Baden HS, Jaworska E, Chang J, Chopra R. Reduced intensity conditioning bone marrow transplan-
[65] Obeid KM. Infections with DNA viruses, adenovirus, poly-
omaviruses, and parvovirus B19 in hematopoietic stem cell transplant recipients and patients with hematologic malign-
[66] Hayashi T, Kohno S, Sato R, Hiraoka T, Ogata Y, Katsuyama K. The prevalence of antibody to human parvo-
[67] Ozawa K, Ayub J, Kajigaya S, Shimada T, Young N. The gene encoding the nonstructural protein of B19 (human) parvo-
[76] Wright C, Hinchliffe SA, Taylor C. Fetal pathology in intra-
uterine death due to parvovirus B19 infection. Br J Obstet Gynae
col 1996;103:133–6.
[78] Yang SH, Lin LW, Fang YJ, Cheng AL, Kuo SH. Parvovirus B19 infection-related acute hepatitis after rituximab-con-