

# Parvovirus-B19 and hematologic disorders

## *Parvovirus B-19 ve hematolojik hastalıklar*

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### Abstract

Parvovirus-B19 (PV-B19) is a member of Parvoviridae, which is one of the smallest DNA viruses. PV-B19-associated diseases usually serve as a good representation of the balance of virus, host response and the immune system. The diseases manifested with PV-B19 are erythema infectiosum, which is common in children, hydrops fetalis, transient pure red cell aplasia in patients with chronic hemolytic anemia, arthralgia - mostly observed in women, and chronic pure red cell aplasia in immunocompromised individuals. Cytopenia (bicytopenia, monocytopenia or pancytopenia) may also accompany the diseases mentioned above. On the other hand, there are many diseases, including neurologic, vasculitic, hepatic, rheumatoid, nephritic, autoimmune, myocardial, and others in which the mechanisms of the diseases are not clear, which may be associated with PV-B19. The virus may manifest with unexpected and unexplained clinical pictures and lead to misdiagnosis. Therefore, hematologic disorders in any unestablished clinical diagnosis should be investigated for PV-B19 infection. However, serologic examination for PV-B19 diagnosis is not sufficient in immunocompromised status. The virus can be determined with polymerase chain reaction (PCR) in the serum or tissue samples. Supportive therapy, blood transfusion and immunoglobulin are the conventional therapeutic interventions for PV-B19 today. Vaccination studies are under examination. (*Turk J Hematol 2010; 27: 224-33*)

**Key words:** Children, hematologic findings, parvovirus, treatment

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### Özet

Parvovirus-B19 (PV-B19) küçük bir DNA virüsü olup Parvoviridae ailesinin bir üyesidir. PV-B19 ile ilgili hastalıklar virus, konakçı cevabı ve immun sistem etkileşmesini temsil eden iyi birer örnektir. PV-B19 ilişkili hastalıklar, çocukluk çağında eritema infeksiözüm, hidrops fetalis ve kronik hemolitik anemilerde geçici eritroid aplazi, kadınlarda artralji, immun yetmezlikli olgularda ise kronik eritroid aplazidir. Sitopeni (bisitopeni, monositopeni yada pansitopeni) yukarıdaki hastalıklara eşlik edebilir. Öte yandan PV-B19 ile ilişkili olabilecek nörolojik, vaskülitik, hepatik, romatoid, nefritik, otoimmun, miyokard hastalıkları ve mekanizması tam olarak açıklanamamış birçok hastalık da vardır. Virus beklenmeyen ve açıklanamayan klinik tablolara yol açabileceği için yanlış tanı konulabilmektedir. Bu nedenledir ki henüz klinik tanı konulmamış, hematolojik bulguları olan hastalarda PV-B19 enfeksiyonu dikkate gelmelidir. Ancak immun yetmezlik durumunda serolojik testler tanı için yeterli olmayabilir. Virus serumda yada doku örneğinde PCR ile tespit edilebilir. Destek tedavisi, kan transfüzyonu yada immunoglobulin günümüzde kullanılan tedaviler olup aşı çalışmaları araştırma aşamasındadır. (*Turk J Hematol 2010; 27: 224-33*)

**Anahtar kelimeler:** Çocuk, hematolojik bulgular, parvovirus, tedavi

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## Introduction

Parvovirus-B19 (PV-B19) was discovered in the mid 1970s by Yvonne Cossart in London [1]. The name of this virus is derived from occupying well B19 in a large series of petri dishes numbered accordingly. Since the discovery of PV-B19, many reports have been published showing an association between the virus and many other clinical diseases [2-10]. In the early 1980s, it was demonstrated as an agent of human disease erythema infectiosum (fifth disease) in children, transient aplastic anemia and hydrops fetalis [3-7]. Gradually, reports showed that this virus had a pathogenic role in a large perspective in addition to sometimes being asymptomatic [8-39]. The literature of PV-B19 infection with a growing number of publications has reported its association with erythema infectiosum in children, transient aplastic crisis in persons with high red cell turnover, chronic pure red cell (PRC) aplasia in primary or secondary immunocompromised patients, hydrops fetalis with infection during pregnancy, and arthropathy, mostly in females. Today, according to the results obtained from PV-B19 studies, in the case of unexpected or unexplained anemia or hematologic disorders, PV-B19 should be investigated. In addition, there are also many diseases with an unusual clinical presentation in which PV-B19 is identified as the pathogen.

In this review, principally PV-B19 and hematologic disorders will be discussed on the basis of the literature and our experience. Special characteristics of the virus are presented beforehand.

### PV-B19 characteristics

Human PV-B19 is from the group Parvoviridae, and is one of the smallest DNA viruses. The Parvoviridae family includes many animal viruses that are pathogenic for animals. Parvoviruses form small capsids about 25 nm in diameter and contain a genome consistent with single-stranded DNA [38-40]. The viral genome encodes three proteins of known function [38-41]. The gene product, the non-structural protein NS1, has been shown to be involved with DNA, helps with replicase function and is cytotoxic for host cells. It also initiates apoptosis with cytokine stimulation. The other two structural proteins, viral protein1 (VP1) and VP2, take part in viral capsid proteins [38,40]. PV-B19 exerts

its pathogenicity by the cellular receptor that is present on erythroid precursor cells and erythrocytes as the blood group P antigen [42]. Since this receptor protein is necessary for viral infection, a person without P antigen on red cells is immune against PV-B19 infection. Various other cells presenting P antigen are platelets and cells on the liver, kidney, heart, lung, endothelium, and on the synovium [43].

PV-B19 infection is seen in all ages worldwide. This infection is common in childhood, and approximately 80% of the population is immune to this virus after 50 years [44]. The infection rate of PV-B19 is determined by assessment of antiparvovirus immunoglobulin (Ig)G antibody in serum samples. The virus is spread by respiratory droplets and has also been transmitted by blood products because of its resistance to heat inactivation and solvent detergents [45,46]. PV-B19 infection is usually asymptomatic. The most common clinical presentations of infection are fifth disease or erythema infectiosum, arthropathy and hydrops fetalis, which are found among immunocompetent hosts [2,3,38]. The infection may cause clinically significant arthropathy in adults, especially middle-aged women. Arthropathy includes not only arthralgia but also inflammatory arthritis that may occur with sequelae in some cases. It may mimic rheumatoid arthritis with clinical presentation and positive rheumatoid factor [34-38,47]. Hematologic diseases such as transient PRC aplastic crisis, hydrops fetalis and single or multiple transient parvovirus-related cytopenias (neutropenia, autoimmune thrombocytopenic purpura, pancytopenia) are also seen in immunocompetent patients [4,5,7-10,39]. Hepatic, neurologic, vasculitic, rheumatologic, and nephritic syndromes, and myocardial disorders associated with PV-B19 are a heterogeneous group of diseases in which the etiological role of the virus is not clear [24-33,36,37,47-55]. Immunocompromised hosts such as cancer patients, transplant patients and/or patients receiving immunosuppressive drugs and those with acquired immune deficiencies are at risk of PV-B19 infection and PRC aplasia resulting in chronic anemia [11-23]. Although erythroid lineage is mostly affected, thrombocytopenia, neutropenia and pancytopenia have also been reported with PV-B19 infection in this group of patients.

Chronic anemia is the result of a selective decrease in red cell precursors in the bone marrow that presents as reticulocytopenia in the peripheral

blood [56-58]. All immunocompromised patients with anemia or any other abnormal hematologic findings, even if they have no specific symptoms of viral infection, should be suspected of PV-B19. Antibody-based diagnostic tests cannot help in the diagnosis because of immunosuppressive status that leads to lower or no Ig production. Virus genome by polymerase chain reaction (PCR) or other assays should be preferred according to patient characteristics [2].

Clinical associations of PV-B19 infection, such as skin eruption or gloves and socks syndrome and chronic fatigue syndrome, are seen rarely [24,59-61]. Intrauterine PV-B19 infection is also very rarely associated with developmental abnormalities [62]. Since the diseases associated with PV-B19 may be related with any system of the body, PV-B19 infection should be kept in mind in cases of an unsolved clinical picture even when there is no suggestion of an infection.

#### **PV-B19 and immune response**

In PV-B19 infection, fever and influenza-like symptoms occur early during viremia. This feature is followed by cutaneous eruption and arthropathy, and this phase corresponds to the appearance of antibody in the blood. While the titers of the virus fall in the blood, IgM antibody appears at the same time and continues for 2-3 months in the serum. IgG antibodies are observed after 2-3 weeks of infection and continue life-long [2,4,61]. The virus can persist in the body for a long time, months and even years [11]. In fact, PV-B19 is eliminated from the patients within a few weeks; however, in 20% of immunocompetent patients and in patients with a defective Ig production against the virus, PV-B19 infection is persistent [11,30,58,61,62]. These patients are a source for PV-B19 infection if they are a donor.

Proteins on the surface of the virus capsids, VP1 and VP2, are recognized by the host immune system and are antigenic determinants. These many linear epitopes due to the VP1 region of the capsid are combined by neutralizing antibodies. VP1 is principally required for an effective immune response and also clearance of the virus. In the early phase of convalescence, the patient's serum reacts to VP2, but it is not effective in the late phase [47,63,64]. Commercial Igs are obtained from the plasma of normal persons with strong anti-VP1 activity.

#### **Hematologic disorders: major hematologic disorders of PV-B19 with underlying disease and conditions**

Parvovirus-B19 is the causative agent of various forms of hematologic diseases, among which transient aplastic crisis in patients with underlying hemolytic anemia, chronic hypoplastic anemia-PRC aplasia in immunocompromised patients and hydrops fetalis in pregnant women are the most common. Besides these hematological disorders, PV-B19 precedes or is associated with other hematological diseases or present hematologic features [39].

**Transient aplastic crisis:** In transient PRC aplasia, PV-B19 has a direct effect on the hematopoiesis, mainly on erythroid progenitor and erythrocytic cell line, and thus anemia is principally the most frequent hematologic presentation. In addition to the increased red cell destruction, patients also produce red blood cells and thus PV-B19 infection may result in transient suppression of erythropoiesis [5-10]. Some patients with clinically inapparent and uncomplicated PV-B19 infection can present with a compensated phase of anemia with a smaller decrease or stable level of hemoglobin. Reticulocytopenia is clear because of cessation of the erythropoiesis in that compensated anemia. Anemia occurs during viremia since PV-B19 infects erythroid progenitor cells, resulting in temporary cessation of red cell production, and lasts about 1-2 weeks. Although specifically erythroid lineage is affected, myeloid lineage, which may also include megakaryocytic cells, may also be suppressed [65-67]. The PV-B19 infection in immunocompetent persons classically presents with an isolated red cell aplasia [5]. However, in immunocompromised patients, the virus can also affect all hematopoietic lineages and lead to pancytopenia [15,58].

Viral infections cause transient bone marrow aplasia or selective erythroid aplasia. Anemia on this basis is rare in healthy subjects without underlying disease because of the long life span of the red blood cell. In contrast, patients with hemolytic anemia can experience a rapid fall in hemoglobin level. Although transient aplastic crisis is self-limited, red cell transfusion as a supportive treatment should be provided in case of acute anemia.

Parvovirus-associated transient hypoplasia of multiple peripheral blood cell lines has also been reported in children with chronic hemolytic anemia and even in healthy individuals [4,9,39,65-67]. In

sickle cell anemia, erythrocyte membrane defects, red cell enzyme defects, thalassemia, and acquired hemolytic anemia result in stressed erythrocyte production as in hemorrhage, iron deficiency anemia and bone marrow transplantation, in which there may be a red cell hemolytic process, and the preceding PV infection can present with transient aplastic crisis [38,39,47]. In a study of a group of sickle cell patients with aplastic crisis, it was shown that nearly all patients had PV-B19 infection close to their crisis [7,8].

In patients with hemolytic anemia, bone marrow examination is not required to establish the diagnosis of aplastic crisis. However, bone marrow aspiration is necessary for a patient who was previously well or has an atypical clinical presentation. The most common finding is normocellular bone marrow with a decrease in erythroblasts [38,39]. It is known that the virus may cause severe pancytopenia and aplastic anemia [68]. A girl from our clinic with PV-B19 infection presenting with a severe aplastic anemia without underlying disease was reported. This patient underwent bone marrow transplantation from her HLA-identical sibling, resulting in complete recovery [69]. Hanada et al. [65] experimentally showed that PV-B19 significantly inhibited erythroid (CFU-E), myeloid (CFU-myeloid) and megakaryocytic (CFU-Mgk) growth in a patient with hereditary spherocytosis. PV-B19-infected patients seem to infer hematological findings as related with their own body physiology and response to virus toxicity.

#### **Persistent PV-B19 infection: chronic pure red cell aplasia**

This clinical aspect of chronic PRC aplasia principally occurs in the context of primary or secondary immune deficiency in patients who cannot produce neutralizing antibody against PV-B19 [12-23,58,70,71]. Since antigen-antibody complexes are not produced in persistent PV-B19, which results in chronic PRC aplasia, fifth disease does not develop. Acquired PRC aplasia was described in a patient with Nezelof syndrome who was infected with PV-B19 infection for the first time [11]. One report suggested that transplacental transmission of PV-B19 caused a severe anemia in three infants [56]. A separate report described three infants with Diamond-Blackfan anemia in whom PV-B19 might have had an unclear role in that hypogammaglobulinemia [57]. Acquired immune deficiency second-

ary to human immunodeficiency virus (HIV) infection [14], immunosuppression occurring in malignant disease or during chemotherapy, and transplantation or autoimmune diseases can lead to chronic anemia due to persistent PV-B19 infection [12-23]. Persistent PV infection in children with leukemia may be associated with anemia or cytopenia and cause prolonged interruption of chemotherapy [70]. Patients who were under chemotherapy for malignant disease such as leukemia may also present PRC aplasia even in remission. The PRC aplasia due to persistent PV infection emerges in the disease course of that patient. However, the two features occur simultaneously only rarely. In the case of PRC aplasia, it is important to investigate and determine PV-B19 in order to prevent any confusion surrounding disease recurrence and interruption of chemotherapy due to suspicion of a toxic effect on the bone marrow. Moreover, PV-B19 should be investigated at the time of the diagnosis of malignant disease [72].

Today, stem cell transplantation of bone marrow and organ transplantation are established therapy methods for many diseases representing both malignant and non-malignant groups. PV-B19 can produce a picture known as PRC aplasia in transplant patients. PV has been identified in patients with engraftment failure due to PRC aplasia [73]. Since the deep immune suppression period continues one year after transplantation, the virus can be increased and more effective in that time [15-23].

#### **Hydrops fetalis**

*In utero*, PV-B19 infection may cause non-immune hydrops fetalis especially during the second trimester of pregnancy [6,38,47,57]. It is known that the fetal red cell source is the liver in the early period of intrauterine life. PV-B19 infection in the liver leads to anemia and also virus, which can directly affect the myocardium and may cause cardiac failure that results in hydrops fetalis [38]. About 10-20% of non-immune hydrops fetalis is related with PV infection [38]. Prospective studies reported a 30% risk of transplacental infection of PV, and it was reported that half of the pregnant women in the German population are susceptible to PV infection [38,47]. On the other hand, many newborns are born from an infected mother without any symptoms. However, death rate among fetuses with hydrops is about 9% [38,47]. Furthermore, in a mother with PV infection in early pregnancy, the

spontaneous abortion rate is reported to be 5%. PV-B19 may also cause premature birth with hematological disorders. Severe anemia in newborns diagnosed as PRC aplasia (Diamond-Blackfan anemia) by bone marrow examination can be the result of transplacental transmission of PV-B19 infection [57]. If a pregnant woman's immune status shows a positive PV-B19 infection via positive IgM antibodies, this mother should be examined by ultrasonography weekly or bi-weekly for at least 10-12 weeks. Amniotic fluid and umbilical cord blood are used to detect the virus and IgM antibodies to PV-B19. Nevertheless, PV-B19 IgM antibody of the mother may be negative at the time of diagnosis of hydrops fetalis. During the follow-up of this fetus, intrauterine transfusion therapy may be necessary.

#### **PV-B19 infection with other hematological disorders**

In addition to the well-known common hematological presentation, PV can present more than the major hematologic manifestations. In this group, the clinical presentation of PV infection can be missed. Based on peculiarities of the host and properties of the pathogen, clinical and hematological symptoms may result in unexpected findings that are not suggestive of PV infection at first evaluation. Since PV-B19 is a hematopoietic, principally an erythrogenic virus, anemia is the most frequent hematologic finding of PV infection. Pancytopenia with mild or masked findings may occur in patients with underlying hemolytic anemia or immunocompromised conditions [8,9,15,39,58]. Autoimmune thrombocytopenia and/or autoimmune isolated neutropenia has been reported in immunocompetent individuals to be caused by or associated with PV-B19 [74,75]. Cartron et al. [74] showed that in 5 of 11 chronic autoimmune neutropenic children, antineutrophil antibody was positive and was an evidence of primary PV infection. Neutropenia and PV association was determined by bone marrow culture studies in another report [4].

Immune thrombocytopenic purpura (ITP) may follow a viral infection or immunization and is caused by an abnormal response of the immune system [76,77]. Antiplatelet antibody production is the main mechanism of ITP. In PV-B19 infection, immune response to the virus is characterized by the appearance of the specific autoantibodies. Host response contributes to the progress of the disease. Persistent infection can be seen in patients who have a low

level of neutralizing antibodies. ITP association with PV-B19 infection was reported by Murray et al. in 1994 [75]. In a study in our clinic of 19 children with ITP (8 acute, 11 chronic), the rate of 47% PV-B19 DNA also indicated a strong association of PV-B19 infection with ITP [78]. This relation was also supported by high seropositivity of anti-PV-B19 IgM and IgG. A literature search revealed case reports of chronic ITP and neutropenia and a case report of sarcoidosis complicated by chronic red blood cell aplasia and severe thrombocytopenia with PV-B19 infection [79-81]. In virus-associated ITPs, antiplatelet antibodies or virus antibody-immune complex has been associated with platelet destruction [75]. In acute ITP cases in whom PV-B19 was detected, a direct antibody-mediated destruction is a likely explanation. The chronic ITP cases with PV-B19 could be associated with autoantibodies or viral persistence. The pathogenic mechanism of thrombocytopenia associated with PV-B19 has been proposed as autoimmune activity and submicroscopic megakaryocytopathic effect leading to less platelet production [78,81,82]. It was also suggested that even stem cells are affected by PV-B19. The three lineage dysplasias in ITP that have been reported from our clinic may be evidence suggestive of the virus effect on stem cells [83].

Acute PV-B19 infection associated with myelodysplastic syndrome (MDS) has been reported rarely in immunocompetent children [84]. Chronic hemolytic anemia or subclinical immune deficiency by contributory predisposing factors with PV-B19 infection might provide the appropriate condition for the outcome of dysplastic presentation. Acute PV-B19 infection mimicking juvenile myelomonocytic leukemia (JMML), classified under MDS, has also been reported [85]. In this case, which was reported from our clinic, clinical and hematological findings strongly suggested JMML, and immunologic examinations were normal. On the basis of this case and a report of PV with myelodysplasia [86], it might be postulated that PV-B19 not only affected the proliferative capacity of hematopoiesis but also the differentiation process, which are the principal findings of MDS, a group of clonal stem cell disorders.

Leukoerythroblastosis characterized by the presence of leukocytosis and erythroid and myeloid blast cells in the peripheral blood in a premature baby was explained to be related to intrauterine PV-B19 infection [87]. Dysplasia restricted to only one lineage such as dyserythropoiesis was reported [88].

There are case reports of PV-B19 infection presenting hemophagocytic lymphohistiocytosis [89,90].

Parvovirus infection with an expanded clinical manifestation may precede or be associated with leukemia. This infection preceding leukemia has been suggested in several reports [72,91,92]. It has been hypothesized that at the time of diagnosis of acute leukemia, the virus may not be present in the serum but may be present at the cryptic site such as the cerebrospinal fluid [91,92]. We experienced two cases of PV-B19 infection and bone marrow infiltration with pre-B cell lymphoblasts in which the diagnosis was established based on morphological and flow cytometric examinations. One of these patients progressed to acute lymphoblastic leukemia (ALL), while the other showed total resolution of the blastic morphology and phenotype in the short follow-up period [72]. A report pointed out the expression of PV-B19 receptor on leukemic cells with a weak association [93]. Temporary effects of the virus on the hematopoietic system may lead to a limited capacity of clonal proliferation, as in our patient with a resolution of ALL. In the case of compromised status of the host, the effect of the virus on hematopoiesis prompts the clonal proliferation, which allows this speculation in our other case with persistent blastic presentation.

### Diagnosis

Constitutional symptoms of PV infection, such as fever and erythroid progenitor cell depletion in the bone marrow, are accompanied by viremia during the first week of infection. PV causes fifth disease in children and polyarthropathy in adults. Transient aplastic crisis occurs in the case of underlying chronic hemolytic anemia conditions, and chronic PRC anemia is presented by persistent infection in immunocompromised individuals. In pregnant women, IgM to PV-B19 is a predictive finding for infection.

Reticulocytopenia occurs at the height of viremia and is followed by anemia according to the host physiology. Bone marrow examination shows normocellularity with findings of profound depletion of erythroid cells, abnormal very large pronormoblasts and normoblasts exhibiting intranuclear eosinophilic inclusion bodies (Lampion or Lantern cells).

Specific antibody IgM begins to appear when the titer of virus falls in the blood and continues for 3-6 months; IgG antibodies can appear in the third week of inoculation of the virus and persist through-

out life. Immunologic assays remain the most sensitive method to detect PV-B19 infection in almost all cases of fifth disease [94,95]. Because of interindividual variation of antibody production according to physiologic conditions, in persistent infection, DNA assay should be performed for diagnosis of PV-B19. In immunocompromised patients, antibody production is minimal or absent. Viral DNA testing is crucial for the diagnosis of PV-B19 infection. PCR can detect PV genome. DNA amplification by PCR assay may be false-positive because of contamination. Real-time PCR is used for determining virus load on tissues, and immunohistochemistry (IH) and *in situ* hybridizations (ISHs) allow the topographical identification of virus-specific target cells in the histological sections. PCR and nested-PCR have been introduced in pathology to detect the PV-B19 genome [95,96].

### Treatment

Clinical approaches to PV-B19 infection should be planned based on the infection symptoms and severity. Infection is self-limited in healthy children and in adults. Isolation is not proposed except for those admitted to the hospital [45]. In patients with chronic hemolytic anemia, blood transfusion may be needed especially in patients with clear spleen sequestration. Blood transfusion is also required in case of intrauterine infection and hydrops fetalis. Specific therapy is adapted according to infection related to the body system and severity of symptoms. Ig therapy has been used in immunocompromised patients and/or autoimmune hematological or non-hematological presentations. Persistent infection in PV is a treatable cause of anemia in immunocompromised patients. Nearly all HIV-infected patients with PV-B19 PRC aplasia responded to therapy with intravenous immunoglobulin (IVIG). This regimen is also curative in patients with congenital immune deficiency [96,97]. Immunocompromised hosts are particularly at risk of PV-B19 infection, including patients with congenital or acquired immune deficiency, acquired immunodeficiency syndrome (AIDS) and cancer, and in transplant patients on immunosuppressive treatment. Ig therapy is effective in ITP patients with a repeated given regimen [98]. Studies regarding vaccination against PV-B19 infection are under way [64,65].

In conclusion, since PV-B19 expresses expanded clinical and laboratory findings, it should be evalu-

ated and kept in mind in patients showing rapid cell destruction, in primary and secondary immune compromised patients, and in pregnant women with any hematological manifestations during their pregnancy. Different clinical findings in any body system with unexplained clinical pictures should also be investigated with satisfactory methods for PV-B19. Investigation of this virus in malignant diseases before starting chemotherapy is an important approach. It is possible that there are more manifestations due to PV-B19 that will be uncovered in the future.

### Conflict of interest

No author of this paper has a conflict of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included in this manuscript.

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