Parvovirus B19 infection mimicking systemic lupus erythematosus, successfully treated with intravenous immune globulin

Sare Gülfem Özlü^{1,*}, Başak Alan², Aysegül Şahiner³, Büşra Bulut⁴, Gülsüm İclal Bayhan⁵, Sonay İncesoy Özdemir⁶

Abstract

Introduction Parvovirus B19 infection generally presents as a transient viral illness in children but rarely shows systemic lupus erythematosus-like symptoms.

Case report Here we present a 7-year-old girl with parvovirus B19 infection who had prolonged fever, rash, pancytopenia and hypocomplementemia making it difficult to differentiate from the first episode of systemic lupus erythematosus. Because she had severe progressive pancytopenia she was administered intravenous immune globulin treatment and her clinical course was dramatically improved.

Discussion Parvovirus B19 infection can mimic systemic lupus erythematosus and it may be difficult to differentiate a recent parvovirus B19 infection and the first presentation of systemic lupus erythematosus. Absence of discoid lesions, alopecia, Raynaud phenomenon and autoimmune hemolytic anemia may help to distinguish parvovirus B19 infection from systemic lupus erythematosus.

Conclusions Parvovirus B19 infection may cause a severe clinical picture resembling systemic lupus erythematosus even in otherwise healthy children. Intravenous immune globulin treatment might be considered in cases resistant to supportive management.

Keywords Parvovirus B19, systemic lupus erythematosus, children

Introduction

Parvovirus B19 (PVB19) infections are associated with a wide spectrum of disease and the most common clinical courses in childhood are erythema infectiosum and aplastic crisis in chronic hemolytic anemias.¹ Adults, especially women, frequently experience arthropathy and there are several case reports documenting the association between PVB19 and various rheumatic diseases.^{1,2} Similarities between

systemic lupus erythematosus and PVB19 infection have also been reported.^{2,3} Additionally, hypocomplementemia without other clinical features of lupus and multisystemic involvement are reported in adults, but these are much rarer in children.⁴ Here we report a 7-year-old girl with PVB19 infection mimicking systemic lupus erythematosus (SLE), successfully treated with intravenous immune globulin (IVIg) administration.

Received: 25 March 2020; revised: 03 May 2020; accepted: 05 June 2020.

¹MD, Associate Professor, Ankara Yıldırım Beyazıt University, Faculty of Medicine, Department of Pediatric Nephrology, Yenimahalle Training and Research Hospital, Yeni Batı Mah., 2026. Caddesi, 2367 Sokak No:4, 06370 Batıkent/Yenimahalle/Ankara, Turkey; ²MD, General Pediatrics Residency, Ankara Yıldırım Beyazıt University, Faculty of Medicine, Department of General Pediatrics, Kızılırmak Mahallesi, 1436.Sokak, Muhsin Yazıcıoğlu Caddesi, Başak Apartmanı, No:2 /26, Çukurambar, Ankara, Turkey; ³MD, General Pediatrics Specialist, Ankara Yıldırım Beyazıt University, Faculty of Medicine, Yenimahalle Training and Research Hospital, Department of General Pediatrics, İnönü Mahallesi, 1794. Sokak, Özmen Park sitesi, No:8 B Blok, Yenimahalle, Ankara, Turkey; ⁴MD, General Pediatrics Residency, Ankara Yıldırım Beyazıt University, Faculty of Medicine, Department of General Pediatrics, Yenibatu Mahallesi, 2413. Sokak, No:6 Kat:3 Batıkent,

Yenimahalle, Ankara, Turkey; ⁵MD, Associate Professor, Ankara Yıldırım Beyazıt University, Faculty of Medicine, Department of Pediatric Infectious Diseases, Mahmut Esat Bozkurt Caddesi, No: 12/3 Çankaya, Ankara, Turkey; ⁶MD, Associate Professor, Ankara Yıldırım Beyazıt University, Faculty of Medicine, Department of Pediatric Oncology, Söğütbeli Caddesi, Aya Sitesi, No: 4/10, Etlik, Ankara, Turkey.

*Corresponding author: Sare Gülfem Özlü, saredr@gmail.com

Article downloaded from www.germs.ro

Published September 2020

© GERMS 2020

ISSN 2248 - 2997

ISSN - L = 2248 - 2997

Case report

A previously healthy 7-year-old girl visited her family physician with fever and sore throat lasting for four days and was started on amoxicillin clavulanic acid treatment with a diagnosis of acute tonsillitis. She was then referred to our hospital because of the persistent fever and maculopapular rash on the second day of treatment. At admission physical examination revealed fever (39°C, axillary) and maculopapular rash involving the whole trunk, extremities and face. The rash was more prominent on extremities (Figure 1).

Figure 1. Maculopapular rash involving the trunk and upper extremities

The oropharynx was hyperemic. Enlarged and painful lymph nodes were detected in the submandibular region. Other systemic examinations were normal. On laboratory examination, white blood cell (WBC) count was $6450/\text{mm}^3$, hemoglobin was 11 g/dL and platelet count was $119000/\text{mm}^3$. Urine examination was normal. Acute phase reactants were mildly elevated; erythrocyte sedimentation rate (ESR) was 37 mm/hour, C reactive protein (CRP) was 5.6 mg/dL (0-0.5 mg/dL). Serum blood urea nitrogen (BUN), creatinine, alanine aminotransferase (ALT), aspartate

aminotransferase (AST), glucose, potassium, magnesium, phosphorus were all in normal range. She had mild hyponatremia (131 mEq/L; normal range: 135-145 mEq/L) and hypoalbuminemia (2.87 g/dL; normal >3.5 g/dL). Chest X-ray was normal. Urine, throat and blood cultures were all sterile. Because the rash had developed after amoxicillin clavulanate exposure, in the first place it was attributed to drug eruption so antimicrobial therapy was switched to clarithromycin. She was still febrile on the third day of hospital admission and rash still persisted. The existence of rash did not correlate with the degree of fever, it was constant and did not respond to antihistaminic drugs. Reevaluating her physical examination revealed hepatosplenomegaly. In repeated laboratory examinations, markedly elevated CRP and ESR, leukopenia, thrombocytopenia and mild anemia were detected; Coombs test was negative. Liver enzymes were mildly elevated as ALT 68 U/L (0-50) and AST 97 U/L (15-60); fibrinogen, ferritin, triglyceride and LDH were all in normal limits. Although all repeated culture samples were sterile, she was started on broad spectrum antibiotics considering the possibility of bacterial sepsis. Abdominal ultrasonography was normal except for hepatosplenomegaly. Echocardiography was normal, there was no coronary artery aneurysm or any other finding suggesting Kawasaki disease. The multisystemic nature of the disease course prompted us to consider connective tissue disorders such as SLE or systemic juvenile idiopathic arthritis. She had a very low complement C4 level as 0.003 g/L (normal range 0.13-0.46 g/L), and slightly low complement C3 level as 0.67 g/L; (normal range 0.82-1.73 g/L). Serum antinuclear antibody (ANA) and anti-double stranded DNA (anti-dsDNA) were negative, also clinically she did not have discoid lesions or alopecia, and she did not have a history of Raynaud phenomenon; so SLE was thought to be unlikely. The distribution of the rash was not associated with the peaks of fever and the duration of the symptoms was less than 2 weeks so systemic arthritis was also excluded. Because she had pancytopenia, fever and rash on the seventh day of her symptoms, viral infections such as measles, rubella, EBV,

CMV and PVB19 were investigated. Among them, specific antibodies to PVB19 IgM and IgG were strongly positive (IgM was 29.1; laboratory index <11 and IgG was 25.1 and laboratory index <11) so the patient was diagnosed as having PVB19 infection. Since the patient had resistant fever, developed pancytopenia and elevated acute phase reactants, and had no improvement in the clinical status on the seventh day of her hospital admission she was administered intravenous immune globulin (IVIg) at a dose of 400 mg/kg/daily for five days. She dramatically responded to IVIg treatment and was afebrile after 24 hours from the first dose. The rash also disappeared after the second day of treatment (ninth day of hospital admission) and did not recur. Platelets, leukocytes and acute phase reactants were completely normal on the fifth day of treatment (twelfth day of hospitalization) and she was discharged with full recovery. On follow up, at the first month after discharge she was symptom-free and complement C3 and C4 levels had returned to normal.

Discussion

There are several reports in adults describing lupus-like features and multisystemic involvements in PVB19 infection but these manifestations are relatively rare in children.^{1,2} Here we presented a 7-year-old girl diagnosed with PVB19 infection mimicking the clinical course of SLE. The first report regarding the relationship between SLE and PVB19 infection was published in 1991 by Meyer et al.³ They presented three patients, one of whom was 15 years old, and they concluded that the presence of PVB19 specific IgM antibody in these patients possibly induced a clinical flare of SLE.³

In 1999, two different pediatric case series were reported.^{5,6} Trapani et al. reported 4 girls aged between 9 and 13 years old and diagnosed with SLE according to American College of Rheumatology (ACR) criteria.⁵ All of them had fever, rash and arthritis at the beginning of the disease; two of them had serositis and ANA was positive in these two patients. Two of the patients also had hypocomplementemia. Pancytopenia, raised ESR, increased muscle and liver enzymes which may be observed in both SLE and

parvovirus B 19 infection were also detected. Diagnosis of PVB19 infection in these patients was established by the presence of specific anti human PVB19 IgM antibodies. Because the clinical manifestations and laboratory anomalies had completely recovered within one year in 3 of the patients, the authors speculated that PVB19 infection could present as a lupus-like syndrome as observed in these three cases.⁵ But the disease course was not self-limited in the fourth patient, she also developed central nervous system involvement during follow-up so they concluded that PVB19 infection had triggered the development of SLE in this patient.⁵

The same year Moore et al. presented 7 children with PVB19 infection mimicking SLE.⁶ At initial admission all of the seven patients had arthralgia/and or arthritis and 6 of them had rash. They also had positive serology suggestive of possible SLE; ANA test was positive in 6 of 7, antibodies to Scl-70 were found in two, antibodies to Sm in one, and antibodies to SS-A and SS-B in one case.⁶ At the end of one year, all children were symptom-free without specific treatment and none of them developed SLE. The authors concluded that when PVB19 infection mimics SLE, the clinical course is much milder than that of true SLE.⁶

In 2005 Sève et al. reported a series of 38 patients including both adults and children.⁷ They stated that the relationship between PVB19 and SLE could be classified into three different situations: PVB19 infection may resemble clinical and laboratory characteristics of SLE, PVB19 may exacerbate previously diagnosed SLE, or SLE may develop following a PVB19 infection. They also specified that the most striking clinical similarities between SLE and PVB19 were arthralgia, malar rash, fatigue, fever, photosensitivity, and serological abnormalities. Hypocomplementemia, anemia, leukopenia, thrombocytopenia, elevated ESR, and production of antinuclear and antiphospholipid antibodies were the most common laboratory similarities. They pointed out that PVB19 infections do not cause discoid lesions, alopecia and Raynaud phenomenon.⁷

The growing evidence on the association of PVB19 and SLE has made the underlying

pathogenesis an area of interest. Although there are many theories in this regard, the most plausible one is that PVB19 infection may trigger production of autoantibodies and these may initiate a transient autoimmunity.⁸ But whether PVB19 mimics SLE or triggers its clinical and laboratory features has not yet been fully understood.⁸

Our patient was admitted with fever lasting for four days. She also had rash that existed for one day and involved particularly the trunk and extremities. She had no clinical or hematological findings of SLE before the onset of parvoviral infection. Fever, rash, hepatosplenomegaly, generalized weakness, anemia, thrombocytopenia, leukopenia, elevated erythrocyte sedimentation rate, low C4 and C3 levels were suggestive of SLE. But the nature of anemia (negative Coombs test, absence of hemolysis), elevated CRP levels, absence of ANA and anti-dsDNA antibodies directed us to evaluate possible infectious diseases, and presence of specific PVB19 IgM and IgG antibodies confirmed the diagnosis of parvoviral infection resembling SLE, rather than a true SLE.

The clinical course was deteriorating despite supportive measurements so she was administered IVIg therapy and dramatical response was achieved after 24 hours. IVIg treatment has already been used in immunocompromised patients infected with PVB19. However, its administration in immunocompetent patients infected with PVB19 is rarely reported. In 2006, Herzog-Tzarfaty et al. reported a 21-year-old previously healthy male who had 3 weeks of fever and profound agranulocytosis due to PVB19 infection and who was successfully treated with IVIg administration.⁹ Authors concluded that patients presenting with acute severe parvovirus infection with a clinical and hematological deterioration who do not respond to common supportive measures may benefit from therapy with IVIg.⁹ The favorable effect of IVIg was attributed to the specific anti-PVB19 antibodies that naturally exist in pooled plasma. It is also suggested that immunomodulatory mechanisms of IVIg particularly triggered by immune complexes may also contribute to its efficacy.^{9,10}

Conclusions

Although controversies exist about the exact pathogenesis underlying the relationship between SLE and PVB19 infection, PVB19 can cause clinical and laboratory features highly suggestive of SLE. It may be challenging to differentiate a recent PVB19 infection and a first presentation of SLE. Absence of discoid lesions, alopecia, Raynaud phenomenon and autoimmune hemolytic anemia and presence of short-lived, low levels of antibodies (particularly ANA, anti-dsDNA) and short-lived fever may help to distinguish PVB19 infection from SLE. IVIg administration should be considered in severe cases with PVB19 infection who are resistant to supportive management.

Consent: Written informed consent was obtained from the parents for publication of this case report and image.

Authors' contributions statement: SGÖ: writing, editing; BA: data collecting; AŞ: resources; BB: data collecting; GİB: methodology, SİÖ: supervision. All authors read and approved the final version of the manuscript.

Conflicts of interest: All authors – none to declare.

Funding: None to declare.

References

1. Valentin MN, Cohen PJ. Pediatric parvovirus B19: spectrum of clinical manifestations. *Cutis*. 2013;92:179-84.
2. Saeki T, Shibuya M, Sawada H, et al. Human parvovirus B19 infection mimicking systemic lupus erythematosus. *Mod Rheumatol*. 2001;11:308-13. <https://doi.org/10.3109/s10165-001-8061-3>
3. Meyer O, Kahn MF, Grossin M, et al. Parvovirus B19 infection can induce histiocytic necrotizing lymphadenitis (Kikuchi's disease) associated with systemic lupus erythematosus. *Lupus*. 1991;1:37-41. <https://doi.org/10.1177/096120339100100107>
4. Hashizume H, Kageyama R. Hypocomplementemia is a diagnostic clue for parvovirus B19 infection in adults. *J Dermatol*. 2017;44:e27. <https://doi.org/10.1111/1346-8138.13469>
5. Trapani S, Ermini M, Falcini F. Human parvovirus B19 infection: its relationship with systemic lupus erythematosus. *Semin Arthritis Rheum*. 1999;28:319-25. [https://doi.org/10.1016/S0049-0172\(99\)80016-X](https://doi.org/10.1016/S0049-0172(99)80016-X)
6. Moore TL, Bandlamudi R, Alam SM, Neshier G. Parvovirus infection mimicking systemic lupus erythematosus in a pediatric population. *Semin Arthritis Rheum*. 1999;28:314-8. [https://doi.org/10.1016/S0049-0172\(99\)80015-8](https://doi.org/10.1016/S0049-0172(99)80015-8)
7. Seve P, Ferry T, Koenig M, Cathebras P, Rousset H, Broussolle C. Lupus-like presentation of parvovirus B19

infection. *Semin Arthritis Rheum.* 2005;34:642-8. <https://doi.org/10.1016/j.semarthrit.2004.07.008>
8. Illescas-Montes R, Corona-Castro CC, Melguizo-Rodriguez L, Ruiz C, Costela-Ruiz VJ. Infectious processes and systemic lupus erythematosus. *Immunology.* 2019;158:153-60. <https://doi.org/10.1111/imm.13103>
9. Herzog-Tzarfati K, Shiloah E, Koren-Michowitz M, Minha S, Rapoport MJ. Successful treatment of prolonged

agranulocytosis caused by acute parvovirus B19 infection with intravenous immunoglobulins. *Eur J Intern Med.* 2006;17:439-40. <https://doi.org/10.1016/j.ejim.2006.02.014>
10. Modrof J, Berting A, Tille B, et al. Neutralization of human parvovirus B19 by plasma and intravenous immunoglobulins. *Transfusion.* 2008;48:178-86. <https://doi.org/10.1111/j.1537-2995.2007.01503.x>

Please cite this article as:

Özlü SG, Alan B, Şahiner A, Bulut B, Bayhan Gİ, Özdemir Sİ. Parvovirus B19 infection mimicking systemic lupus erythematosus, successfully treated with intravenous immune globulin. *GERMS.* 2020;10(2):244-248. doi: 10.18683/germs.2020.1211