Purpuric rash in an adolescent with fever, pancytopenia, and an hemophagocytic lymphohistiocytosis-like syndrome due to parvovirus B19

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Abstract
A rare case of parvovirus B19 infection associated with fever, hemorrhagic rash, and a clinical course resembling an incomplete HLH syndrome is presented. Parvovirus B19 should be included in the evaluation of febrile purpura and HLH-like syndrome.

KEYWORDS
children, parvovirus B19, purpuric rash, HLH

1 | INTRODUCTION

Parvovirus B19 infection is very common and occurs worldwide either sporadically or in outbreaks during late winter and early spring. Infection rates peak in childhood, but it is not uncommon in adulthood; up to 85% of adults are positive for parvovirus IgG antibodies, indicating past infection.[1,2] Although the majority of persons with parvovirus B19 infection are asymptomatic or have mild, nonspecific, cold-like symptoms, there are five well-established syndromes associated with parvovirus B19: erythema infectiosum, polyarthropathy syndrome, fetal infection leading to nonimmune hydrops fetalis or intrauterine fetal death, pure red cell aplasia (PRCA) in immunocompromised individuals, and aplastic crises in patients with hemolytic anemia.[3]

In this case report, we present an atypical case of parvovirus B19 infection in a 15-year-old patient with purpuric rash, fever, pancytopenia, and an HLH-like syndrome due to parvovirus B19.

2 | CASE PRESENTATION

A 15-year-old previously healthy boy was admitted to our clinic after a 3-day course of fever, an expanding erythematous

hemorrhagic rash, and malaise. The child mentioned a possible insect bite while he was on vacation, in July 2019. At the trauma site, he developed mild itching and an erythematous confluent rash. A few hours later, the rash became hemorrhagic and the patient developed fever with rigors.

He was first examined at a rural hospital where he received a short course of amoxicillin/ clavulanic acid, as for cellulitis, but without improvement. His hemorrhagic rash disseminated to other areas of the body, and his general condition gradually deteriorated. The child started receiving vancomycin, clindamycin, and ceftriaxone for potential sepsis. He was then transferred to our tertiary center for further evaluation and management.

On admission, he was febrile ($T = 38.1°C$) and fatigue, with a red throat and a rash. His level of consciousness was good. No other abnormal findings were detected. The clinical presentation can be described as follows: confluent erythematous rash with hemorrhagic lesions occupying the inguinal and femoral regions plus hemorrhagic lesions in the armpits and the bilateral extremities (Figure 1). The hemorrhagic rash disseminated to the dorsal surfaces of the palms and soles of his feet. His blood examinations on admission revealed a hemoglobin (Hb) of 9.4 g/dL, white blood cell

count (WBC) of 2.11×10^9/L with mild neutropenia (neutrophil absolute number (NAN) = 1.32×10^9/L), platelets of 108×10^9/L, a prolonged prothrombin time (PT) of 16.8 seconds/ INR = 1.46, C-reactive protein (CRP) of 71.5 mg/L, and lactate dehydrogenase (LDH) of 662 U/L. Antimicrobial therapy was scaled down to vancomycin and ceftriaxone.

During the first two days of hospitalization, he was still febrile (maximum $T = 39°C$) with rigors and fatigue, with facial pallor and a few new hemorrhagic lesions in the upper and lower extremities. Blood tests were deteriorating: Hb gradually decreased to 7.6 g/dL with low retics 0.2%, WBC reached 1.38×10^9/L with severe neutropenia (NAN = 0.32×10^9/L), platelets = 75×10^9/L, INR = 1.43, and a ferritin of 1691 ng/mL. CRP fell to 20.5 mg/L, and LDH was 664 U/L. Immunoglobulin levels were within the normal range, and blood and urine cultures were negative. His antibiotic regimen was then amended to vancomycin and piperacillin/tazobactam due to the profound neutropenia, and doxycycline was added to cover for possible rickettsial infection because of the initial history of a possible insect bite. Deterioration of the patient increased clinical suspicion for more severe underlying pathology such as malignant disease, hemophagocytic lymphohistiocytosis (HLH), and autoimmune disease. The abdominal ultrasound revealed mild hepatosplenomegaly, and the chest X-ray (CXR) was clear. Finally, after discussion with the pediatric hematologists, the boy received a course of intravenous immunoglobulins (IVIGs) at a dose of 1 g/kg on the 3rd day of his hospitalization.

On the 4th day of his hospitalization, an even lower Hb value of 7 g/dL was recorded and he received red blood cell (RBC) transfusion. On the same day, WBCs = 1.8×10^9/L (NAN = 0.481×10^9/L), platelets = 114×10^9/L, INR = 1.2, and CRP = 26 mg/L. Ferritin increased to 1802 ng/mL. His liver enzymes remained normal. On the fifth day of hospitalization (day 8 of his illness), that is, one day after IVIG administration, he remained afebrile, his general condition started improving, and his exanthem started to regress.
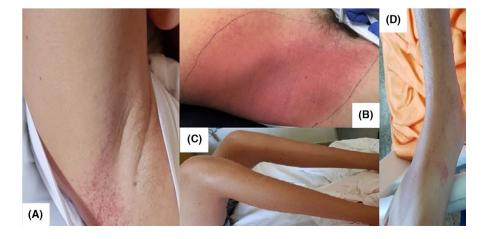
Overall, his blood and urine cultures were negative for bacteria, in addition to the serology for cytomegalovirus (CMV), Epstein-Barr virus (EBV), *Rickettsia typhi, Rickettsia conori,* and toxoplasma. CD25-soluble antigen, autoantibodies, and Leishmania serology were also negative. Examination of stained thick and thin blood films for malaria gave negative results as well. Molecular studies of the blood and bone marrow were negative for adenovirus, CMV, herpes simplex virus ½ (HSV1/2), EBV DNA, enterovirus RNA, and human herpesvirus 6 (HHV6) DNA. The bone marrow and the peripheral smear examination revealed no malignant cells but rather pointed toward aplasia of the erythroid series possibly due to viral infection. Despite the abundancy of macrophages in the bone marrow (BM), there was no evidence of hemophagocytosis. The PCR test for leishmania parasites was also negative. PCR for Parvo B19 DNA was found strongly positive in serum and plasma and in the bone marrow. IgG and IgM antibodies against parvovirus B19 were also positive in serum (Table 1).

The boy was hospitalized for a total duration of 11 days, until accomplishment of the complete recovery of erythropoiesis in the bone marrow. His exanthem had almost completely faded by the 8th day of hospitalization; however, mild hyperpigmentation was evident. The child was overall clinically well and was discharged with some mild splenomegaly persisting. The full blood count (FBC) obtained 10 days after discharge was normal. Hepatosplenomegaly regressed as shown in the abdominal ultrasound 30 days after discharge.

3 | DISCUSSION

Around 25% of infected immunocompetent patients will be completely asymptomatic, and 50% will only have nonspecific flu-like symptoms. The remainder will develop the typical rash of erythema infectiosum usually in combination with arthralgias.[4,5] The typical rash of erythema infectiosum

FIGURE 1 Hemorrhagic rash on the trunk and extremities of a 15-year-old boy with parvovirus B19 infection. (A) Right armpit, (B) right iliac region, (C) lower extremities, and (D) right tibia and dorsal foot

TABLE 1 Major laboratory findings during hospitalization

	Hb (g/dL) 13.5-17.5	White blood cells (*10⁹/L) 4.5-13.5	Neutrophil absolute number (NAN) 1800-8000	Platelets (*10⁹/L) 150-300	C-reactive protein (mg/dL) 0-5	Ferritin (ng/dL) 20-250	INR 0.85-1.15
On admission	9.4	2.11	1320	108	62		1.5
Day 1	9	1.41	620	63	71.5	1113	1.42
Day 3	7.6	1.38	320	75	26.6	1802	1.13
Day 4	7	1.85	480	71	16.9	1412	1.2
Day 7	9.9	4.64	2213	110	6.4	673	1.2
Day 10	10.2	6.48	3512	230	7.5	459	1.1

comprises an erythematous malar rash on the face usually followed by a characteristic reticulated or lace-like rash on the trunk, the hands, and the feet.[6] Parvovirus B19 infection may cause an arrest of the erythroid cells' maturation in the bone marrow. In immunocompetent persons, this results in a transient mild decrease in hemoglobin levels, whereas among immunocompromised patients chronic aplastic anemia may develop. In addition, infection in patients with hemoglobinopathies may also trigger an aplastic crisis.[3,6]

Even though the infection occurred in a previously healthy child, there were some atypical characteristics. The rash was not the typical rash associated with erythema infectiosum. It commenced as an intense confluent well-demarcated erythematous rash with purpuric lesions on both inguinal areas with itching. The purpuric rash later disseminated to cover the extremities and the armpits. The association of purpuric rash with parvovirus B19 has been described in the papular-purpuric gloves and socks syndrome (PPGSS) and in some other purpuric rashes with atypical distribution.[6-8] The distribution of the rash in PPGSS consists mainly of edema and redness of hands and feet followed by the eruption of petechial and/ or purpuric lesions mainly on the palms and soles but also on the dorsal aspects of distal extremities. On rare occasions, it may also involve the elbows and knees. There is usually a demarcated edge of the rash on the wrists or ankles.[9] There have been few cases of PPGSS described in the literature.[10] In this case, the purpuric rash appeared on the hands and feet including the dorsal areas of palms and soles which is characteristic for PPGSS. However, it was also prominent bilaterally on the inguinal areas and the axillae. The initial confluent erythematous rash on the inguinal areas in combination with the history of a possible vector bite initially guided our diagnosis and part of the treatment toward one of the rickettsial diseases endemic in the Mediterranean basin, that is, *Rickettsia conori* infection.[11] However, the negative serology excluded these diseases. This rash cannot be characterized as a case of IgA vasculitis (Henoch Schonlein purpura) because of the atypical distribution of the rash, that is, complete absence from the buttocks,

the presence of high fever, and pancytopenia.[12] During the early stages of presentation, meningococcemia was also considered as a possible diagnosis because of the combination of the purpuric rash with the high fever, the deteriorating clinical condition of the child, and the persistently prolonged INR that raised fears of possible dissemination to intravascular coagulation (DIC). The negative findings of the blood cultures made this diagnosis less plausible.[13] Immune thrombocytopenia (ITP) could not have been the cause of the hemorrhagic rash as the platelet count was >100 000 × 10⁹/L when the first purpuric lesions appeared; the absence of bruises and epistaxis and the presence of hepatosplenomegaly were also not consistent with ITP.[14] Therefore, the most likely diagnosis of the rash was an atypical manifestation of the PPGSS by the virus. Three more cases have been described in the literature with atypical rash in the context of PPGSS caused by parvovirus B19 infection.[10]

The severe presentation of this child could have been the early stage of a possible HLH. Our case had four of the five criteria required for the diagnosis of HLH based upon the diagnostic guidelines for HLH syndrome (HLH-04) issued by the Histiocyte Society in 1991 and updated in 2004.[15] However, in this case there was a high persistent fever, cytopenia in all three lineages, elevated ferritin levels well above 500 ng/mL, and hepatosplenomegaly on the ultrasound. The NK cell activity was not tested as our laboratory does not offer this service. Despite fibrinogen levels were within the normal range, there was a PT prolongation possibly reflecting early signs of liver's function failure. It is also well recognized that hemophagocytosis in the BM is not an early sign of HLH.[16]

There are approximately 30 cases of HLH triggered by parvovirus B19 reported in the literature thus far.[16,17] It appears that in the majority of these cases, the patients survived without any specific therapy for HLH, which shows that the parvovirus-triggered HLH carries a better prognosis.[16]

It is possible that the prompt administration of IVIG reversed the situation at an early stage by alleviating the manifestations of the infection. IVIG has been proven to be

effective in the treatment of PRCA in patients suffering from chronic infection by parvovirus B19,[18] and its use is mainly limited to these patients. However, there is evidence of effectiveness of IVIG in the treatment of non-PRCA manifestations such as in cases of neutropenia or thrombocytopenia and systemic vasculitis.[19,20]

The pathophysiology of virus-induced HLH is not clearly understood. However, it seems to trigger the interaction between T cells and macrophages, which leads to the persistent activation of lymphocytes. This causes a hypersecretion of pro-inflammatory cytokines such as IFN-γ, TNF-a, IL-6, IL-8, IL-10, and IL-18.[16] Acute infection by parvovirus B19 can cause an inflammatory response characterized by the activation of immune cells and hypersecretion of cytokines. In this process, NS1 protein of the virus appears to have a major role as it transactivates pro-inflammatory cytokines such as TNF-alpha and IL-6.[3,21,22] Further to this, the stimulated lymphocytes can produce IL-2 and IFN-γ in response to other proteins of the virus namely VP1/VP2.[22,23] These could all contribute to hypersecretion of cytokines and the induction of HLH during an infection by the virus.

4 | CONCLUSION

Parvovirus B19 should be included in the evaluation of febrile purpura and in HLH-like syndrome with fever and purpuric rash.

CONFLICT OF INTEREST
There is no conflict of interest for any of the authors.

AUTHOR CONTRIBUTION
All three authors: contributed to the design of the report and reviewed, corrected, and approved the final form of the manuscript. MC: wrote the first draft of the introduction. AT and MK made: the draft for the case description, and MK: wrote the draft of the discussion.

ETHICAL APPROVAL
Informed consent was obtained from the parents of the child. Personal data were not disclosed in the manuscript.

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