

Original Article

## Spontaneous Resolution of Hemophagocytic Syndrome and Disseminated Intravascular Coagulation Associated with Parvovirus B19 Infection in a Previously Healthy Child

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**SUMMARY:** A 10-year-old male with a brain abscess developed pancytopenia, liver dysfunction, disseminated intravascular coagulation (DIC) and decrease of immunoglobulin A (IgA) level during postoperative antibiotic and anticonvulsant therapy. A bone marrow examination revealed hemophagocytosis. Real-time PCR revealed parvovirus B19 infection. The hemophagocytic syndrome resolved without specific treatment. To our knowledge, this is the first report of a spontaneous resolution of parvovirus B19-associated hemophagocytic syndrome and DIC.

### INTRODUCTION

Virus-associated hemophagocytic syndrome (VAHS) is a rare disorder characterized by macrophage activation and proliferation. Activated macrophages in bone marrow engulf erythrocytes, leukocytes, platelets and their precursors, causing cytopenia. The diagnostic criteria of VAHS include clinical signs such as fever, hepatosplenomegaly, lymphadenopathy, and rash, and laboratory findings such as pancytopenia, liver dysfunction, disseminated intravascular coagulation (DIC), hypertriglyceridemia, and bone marrow changes. VAHS is usually associated with a number of systemic viral infections, particularly with Epstein-Barr virus (EBV) (1-3), and occasionally occurs in association with parvovirus B19. The patients usually recover in weeks with antimicrobial therapy, or in some cases the syndrome resolves naturally. To our knowledge, this is the first report of a spontaneous recovery of parvovirus B19-associated VAHS in the presence of DIC in childhood.

### PATIENT AND LABORATORY INFORMATION

A 10-year-old boy was admitted to our hospital with a complaint of numbness and weakness on the left side of his body over the previous 3 days. On examination he was found to have left hemiplegia and facial palsy. Cranial tomography showed a mass of 4 cm diameter appearing as a ring-enhancing lesion and indicating an abscess cavity on the right parietal lobe. The abscess was drained by open surgery, and a combination antimicrobial treatment with ornidazole, vancomycin, meropenem, and phenytoin as an anticonvulsant was started. Phenytoin was given at 5 mg/kg/day in two divided doses for 3 weeks after surgery. Preoperative laboratory findings, including complete blood count, liver and renal function tests, coagulation parameters and serum immunoglobulin levels, were within the normal range. Histopathological analysis of the brain specimen strongly suggested an abscess with infiltration of predominantly neutrophils. No atypical cells were seen. A culture of the abscess material did not show bacterial growth. One week later, the child's condition suddenly wors-

Table 1. Patient's clinical course including coagulation and fibrinolysis

Date D/M/Y	Time	Therapy	Hb (gr/dl)	WBC (mm <sup>3</sup> )	Plt (mm <sup>3</sup> )	ANS	PT (sec)	PTT (sec)	Fib (mg/dl)	FDP	D-dimer	IgA (mg/dl)
20/11/02	Preopt	Ab	12	5,600	249,000	3,560	12	30	236	-	-	86
28/11/02	Postopt 5 days	Ab, Phen	9.7	5,400	250,000	3,200	12	32	326	-	-	
30/11/02	Postopt 7 days	Ab, Phen	10	4,370	94,500	2,400	14	34	168	-	-	
02/12/02	Postopt 10 days	Ab, Phen	9.9	3,100	73,000	1,640	15	35	172	-	-	
03/12/02	Postopt 11 days	Ab, Phen	7.9	2,400	9,100	1,230	16	31	112	21	5	
04/12/02	Postopt 12 days	Ab, Phen FFP, Plt conc.	6.4	1,400	3,280	560	16.7	39	73	28	7.4	26
05/12/02	Postopt 13 days	Ab, Phen	6.2	3,100	7,400	1,200	14.3	34	100	21	8	
06/12/02	Postopt 14 days	Ab, Phen	6.4	3,370	6,920	1,500	14	30	180	14	7	13
07/12/02	Postopt 15 days	Ab, Phen	7.8	3,880	16,200	2,100	14	24	194	5	1	
09/12/02	Postopt 17 days	Ab, Phen	8.9	5,460	168,000	2,500	14	28	240			

Ab, antimicrobial therapy; Phen, phenytoin; FFP, fresh frozen plazma; Plt conc, platelet concentrate; Hb, hemoglobin; WBC, white blood cell; ANS, absolute neutrophil count; PT, prothrombin time; PTT, partial thromboplastin time; Fib, fibrinogen; FDP, fibrin degradation product; IgA, immunoglobulin A.

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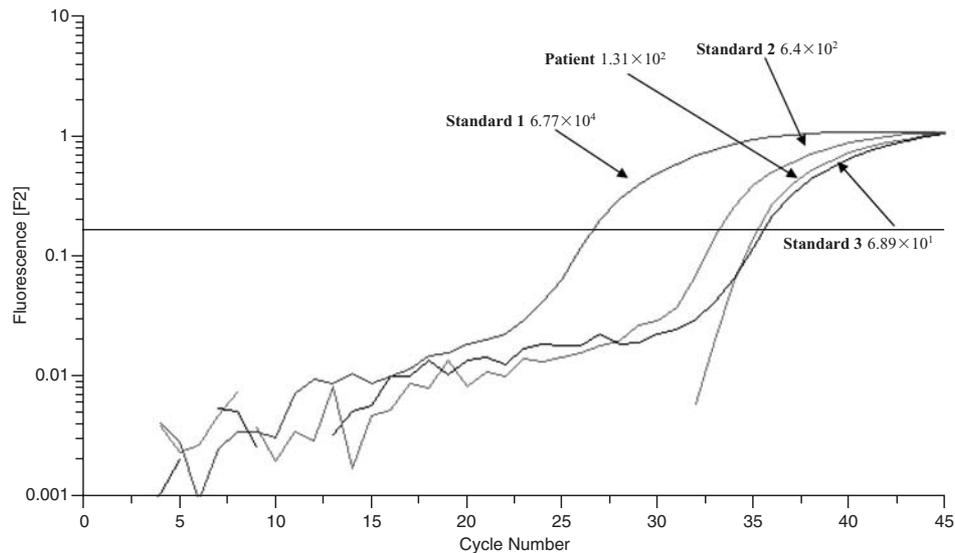


Fig. 1. Real-time PCR result for parvovirus B19 in patient serum sample.

ened. He developed high fever that rose as high as 40.5°C, generalized lymphadenopathy, hepatomegaly, splenomegaly, bilateral facial rash and generalized maculopapular eruption all over the body. Laboratory investigations revealed elevated liver enzymes, pancytopenia and coagulopathy (Table 1). The serum levels of triglyceride, lactic dehydrogenase and ferritin were 283 mg/dl, 832 U/l and 526 mg/dl, respectively. The serum IgA level declined to 13 mg/dl (normal range: 60-294), while the IgG and IgM levels were within the normal limits. Blood, throat, and urine cultures were negative. The serum was weakly positive for anti-parvovirus B19 IgM and negative for anti-parvovirus B19 IgG, but 5 days later, positivity for anti-parvovirus B19 IgG was apparent. A very low level of parvovirus B19 positivity was detected in the serum,  $1.31 \times 10^2$  copy/reaction (2,600 copy/ml) by a very sensitive, commercially available real-time PCR assay with a lower detection limit of 10 copies per reaction (Light Cycler, Parvovirus B19 Quantification Kit, Mannheim, Germany) (Fig. 1). None of the other viral (EBV, cytomegalovirus, hepatitis A virus, hepatitis C virus, rubella) serological markers were positive. Bone marrow aspiration showed numerous macrophages engulfing erythrocytes, leukocytes, platelets and their precursors and giant normoblasts. Platelet and fresh frozen plasma were given only once to stop gingival bleeding. Antimicrobial and phenytoin therapy were continued for a total of 3 weeks, during which the clinical and laboratory abnormalities recovered gradually.

## DISCUSSION

Parvovirus B19 infection occurs in 50% of children under the age of 15 worldwide and is known as the cause of erythema infectiosum. However, a wide variety of hematological manifestations can be observed during the course of parvovirus B19 infection, including transient aplastic crisis in patients with chronic hemolytic anemia and immunodeficiency diseases and, rarely, hemophagocytic syndrome (4,5). The diagnosis of VAHS is made by characteristic bone marrow morphology in the presence of typical clinical and laboratory abnormalities. Thus, in the present case, hemophagocytic syndrome was diagnosed based on the presence of high fever, generalized lymphadenopathy, hepatosplenomegaly,

and maculopapular eruption in association with pancytopenia, liver dysfunction, DIC, hyperferritinemia, hypertriglyceridemia, extensive hemophagocytosis, and proliferation of histiocytes in bone marrow. Positive anti-parvovirus B19 serology and PCR analysis suggested that hemophagocytic syndrome may be caused by this virus. The child was also taking phenytoin. Hemophagocytic syndrome has been reported in a 9-year-old boy receiving phenytoin, but he was not tested for parvovirus B19 despite the fact that fever, erythematous rash and lymphadenopathy indicated this infection. Therefore, the role of phenytoin in the pathogenesis of hemophagocytic syndrome is not yet clear (6).

There have been a total 22 cases of parvovirus B19-associated hemophagocytic syndrome reported so far (7,8). Nine of these were children, and 3 of the 9 recovered spontaneously. However, none of these spontaneously recovered children had DIC, which is a severe complication of VAHS resulting from cytokine-induced tissue factor release (9). Elevated levels of cytokines such as tumor necrosis factor-alpha (TNF- $\alpha$ ) and interleukin-1 (IL-1) are associated with the severity of manifestations in VAHS (10). Unlike these cases, our patient had DIC but showed spontaneous recovery without specific treatment for parvovirus B19, such as intravenous immunoglobulin. In our case, brain tissue injury due to surgical drainage of the abscess may also have contributed to the development of DIC (11). We think that the clinical improvement of our patient was neither due to occurrence of anti-parvovirus B19 antibody nor due to transfusion of a single unit of fresh frozen plasma and platelet concentrate for gingival bleeding.

Although hemophagocytic syndrome can occur in the setting of congenital or acquired immunodeficiency, our patient had no clinical or laboratory evidence of underlying immunodeficiency. The marked decrease in serum IgA level observed during the hemophagocytic syndrome may have been due to the phenytoin use or to the hemophagocytosis itself, since the level returned to normal 2 months later (12,13). A decrease of serum immunoglobulins may complicate the course of the disease by enhancing the susceptibility to infection and therefore should be closely followed up.

To our knowledge, this is the first report of spontaneous resolution of parvovirus B19-induced hemophagocytic

syndrome associated with DIC in a previously healthy child. Parvovirus B19 mainly infects normoblasts, is usually associated with a milder inflammatory response than EBV or other viruses, and can cause markedly elevated inflammatory cytokines and acute-phase reactants, leading to severe hemophagocytic histiocytosis requiring immunosuppressive or antiviral therapy.

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