

CASE REPORT

PARVOVIRUS B19 INFECTION PRESENTING AS ACUTE HEPATITIS AND TRANSIENT ANEMIA IN A PREVIOUSLY HEALTHY CHILD

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Abstract. Acute hepatitis has been noted as a manifestation of parvovirus B19 infection in children and adults, although its pathogenesis remains unclear. In this report, we present a case of an 11-year old Thai boy with parvovirus B19-associated acute hepatitis who presented with jaundice, hepatomegaly and transient aplastic crisis. Our report underscores the need to consider parvovirus B19 as the causative pathogen in patients with increased liver enzymes, jaundice and anemia.

Keywords: parvovirus B19, hepatitis, anemia, aplastic crisis, healthy child

INTRODUCTION

Human parvovirus B19 is a member of the *Erythroparvovirus* genus and the Parvoviridae family. It is a non-enveloped icosahedral virus with a single-stranded DNA genome (Young and Brown, 2004). Globoside, also known as the erythrocyte P antigen, is a cellular receptor for parvovirus B19 (Brown *et al*, 1993). P antigen is found on erythroblasts, megakaryoblasts, endothelial cells, fetal myocytes, and placental trophoblasts (Simon, 2008).

Parvovirus B19 is transmitted mainly by respiratory droplets and outbreaks often

occur among school-aged children (Servey *et al*, 2007). Viral infection from blood or blood products and direct transmission vertically in utero have been reported (Brown, 2010). Erythema infectiosum, which manifests as “slapped cheek” or innocuous rash illness, is the most common clinical manifestation of infection with parvovirus B19 (Valentin and Cohen, 2013). Other clinical findings associated with infection include arthralgia and arthritis, aplastic crisis in patients with red blood cell defects, chronic anemia in immunocompromised patients, fetal hydrops, cardiac disease, neurologic and hepatic diseases (Broliden *et al*, 2006). Although parvovirus B19 infection resulting in acute hepatitis is uncommon, it should be considered in cases presenting with jaundice and anemia or cases who test negative for other hepatotropic viral pathogens.

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CASE REPORT

An 11-year old previously healthy Thai boy was seen in the emergency department with high-grade fever, vomiting, icteric sclerae and fatigue. He had been sick for 3 days and during that time had been given paracetamol 15 mg/kg/dose twice daily and ibuprofen 10 mg/kg/dose twice daily.

On admission, his axillary temperature was 38.6°C. He was slightly pale with noticeable jaundice and hepatomegaly (5 cm below the right costal margin). His body weight was 48.2 kg, his height was 146 cm, and his Body Mass Index (BMI) of 22.6% was in the "at risk for overweight" category (Barlow and the Expert Committee, 2007). No significant lymphadenopathy or splenomegaly was palpable and the rest of the examination was unremarkable.

Laboratory tests on admission were: a leukocyte count of 7,200 / μ l (39.9% lymphocytes, 46.3% neutrophils), a hemoglobin of 9.3 g/dl (11-13.5 g/dl), a mean corpuscular volume (MCV) of 74.9 fl (80-100 fl), a platelet count 151,000/ μ l (150,000-350,000/ μ l), an aspartate aminotransferase (AST) level of 1,084 U/l (15-40 U/l), an alanine aminotransferase (ALT) level of 2,673 U/l (10-35 U/l), a total bilirubin level of 9.04 mg/dl (0.1-1.5 mg/dl), a direct bilirubin level of 6.48 mg/dl (0-0.2 mg/dl) and an alkaline phosphatase level of 319 U/l (100-390 U/l). Hemoglobin electrophoresis showed heterozygous hemoglobin E (HbE) or HbE trait.

An abdominal ultrasound showed hepatomegaly but the liver was otherwise normal appearing. Serum collected on the fifth day of illness was positive for parvovirus B19 IgM and IgG. A polymerase chain reaction (PCR) for parvovirus B19 was positive for the viral NS1 gene. Sequence analysis of the latter revealed

it was genotype 1 (accession number KJ855149). Serological tests for Epstein-Barr virus (EBV), cytomegalovirus (CMV), hepatitis A, B, C and E virus and human herpes virus 6 were negative.

This boy presented with classic symptoms of acute hepatitis with laboratory-confirmed parvovirus B19 infection. Other common viral pathogens tested for were negative. A detailed interview did not indicate a history of toxin ingestion, another possible cause for acute hepatitis. Although this boy was initially treated with paracetamol, which could potentially cause drug-induced hepatitis, this hypothesis is unlikely since the duration of treatment was short and the dosage was correct.

Table 1 shows the laboratory results for this patient on admission and at follow-up. His liver enzymes decreased by 2 weeks (AST 57 U/l, ALT 190 U/l). He developed transient aplastic crisis when the hemoglobin decreased by more than 2 g/dl (9.3 to 7.2 g/dl). He became afebrile by the sixth day of hospitalization and had clinical improvement by a week. His liver enzymes were still slightly elevated 45 days after the onset of symptoms (AST 48 U/l, ALT 102 U/l). This may be due to non-alcoholic fatty liver disease (NAFLD), which can be found in overweight children. His hemoglobin level rose to 11.0 g/dl by the two-month follow-up visit.

DISCUSSION

Acute hepatitis can be caused by infectious agents, toxins, drugs, autoimmune or metabolic diseases. Viruses are the most common infectious causes of acute hepatitis, the majority being hepatitis A-E (Jain *et al*, 2013). Dengue virus, herpes virus, Epstein Barr virus, cytomegalovirus and parvovirus B19 can

Table 1
Liver function test and blood cell counts of the patient on admission and at the follow-up visits.

Laboratory values	Day 3	Day 5	Day 6	Day 9	Day 14	1.5 months	2 months
Albumin (g/dl)	3.6	3.3	3.4	3.9	4.1	-	-
Total bilirubin (g/dl)	9.04	10.52	9.63	3.44	2.00	0.64	-
Direct bilirubin (g/dl)	6.48	7.72	7.06	2.32	1.30	0.17	-
AST (U/l)	1,034	160	85	99	57	48	-
ALT (U/l)	2,673	1,087	763	459	190	102	-
ALP (U/l)	319	289	312	434	335	313	-
GGT (U/l)	169	-	-	-	71	-	-
Hemoglobin (g/dl)	9.3	8.0	7.2	8.7	-	-	11.0
Hematocrit (%)	27.9	25	22.8	28.4	-	-	34.6
Corrected reticulocyte (%)	-	-	1.5	-	-	-	1.1
MCV (fl)	74.9	76	77	79	-	-	74.8
Leukocytes (/μl)	7,200	8,110	7,370	6,520	-	-	12,220
Platelets (/μl)	151,000	172,000	207,000	463,000	-	-	301,000

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma glutamyl transferase; MCV, mean corpuscular volume.

also cause acute hepatitis. In Thailand, the prevalences of the various etiologies of acute hepatitis are limited; however, hepatitis A and B were found to be the most common pathogens causing acute hepatitis among Thai children and adults in one study (Pongpan, 2012). The seroprevalence of hepatitis A in Thailand has decreased among children, adolescents and young adults over the past decade due to better hygiene and sanitation (Ri-anthavorn *et al*, 2001). The high coverage rate of hepatitis B immunization over the past 20 years as part of the EPI program has resulted in a drastic reduction of hepatitis B carrier to 0.7% among children who were born under the program (Chongsri-sawat *et al*, 2006).

Acute hepatitis is an uncommon manifestation of parvovirus B19 infection and often overlooked due to infrequent testing and lack of awareness. About 50 cases of parvovirus B19-related hepatitis

have been reported worldwide (Bihari *et al*, 2013). Most cases presented with acute hepatitis and some progress to fulminant hepatitis and liver failure, especially with co-infection with other hepatotropic viruses (Dwivedi *et al*, 2009). The outcome of most acute hepatitis cases caused by parvovirus B19 is complete spontaneous resolution (Sokal *et al*, 1998).

Two mechanisms have been proposed to explain how parvovirus B19 causes hepatitis. The first mechanism is the direct cytopathic effect of B19 on hepatocytes. A non-structural protein (NS1) located on the N-terminal region of the B19 genome is believed to be associated with apoptosis of hepatocytes and erythrocyte progenitor cells (Morita *et al*, 2003). The second mechanism is an indirect immunological effect, whereby circulating CD8+ cytotoxic T cells proliferate and secrete IFN- γ and TNF- α against parvovirus B19 infected hepatocytes. Increased circulating cytotoxic

T cells lead to defective monocyte and macrophage differentiation, reduction in circulating IL-1 levels and increased TNF- α , IFN- γ and IL-2 receptors. These changes alter the hepatic microenvironment resulting in damage to hepatocytes causing acute hepatitis (Andreesen *et al*, 1989; Muta *et al*, 2008; Rauff *et al*, 2011).

Our patient experienced transient aplastic anemia on the sixth day of illness. His hemoglobin reached 7.2 g/dl, dropping by 2.1 g/dl in 3 days (Table 1). A low corrected reticulocyte count suggests ineffective erythropoiesis. Since parvovirus B19 has a tropism for erythrocyte progenitor cells, it inhibits erythropoiesis for a short time and this inhibition resolves after viral clearance by neutralizing antibodies (Brown and Young, 1996). The transient decrease in the production of erythrocytes results in a decrease in the hemoglobin concentration (Mustafa and McClain, 1996; Bihari *et al*, 2013). Although there have been case reports of anemia secondary to B19 infection developing in patients without underlying diseases (Lugassy, 2002; Qian *et al*, 2002; Mishra *et al*, 2005), this condition is usually self-limited in immunocompetent individuals (Mustafa and McClain, 1996). Our patient had no known underlying hematologic diseases and hemoglobin typing showed only HbE trait. After the resolution of the infection, his hemoglobin returned to normal. There is no specific treatment for parvovirus B19 infection. The symptoms and elevated liver enzymes usually resolve by themselves (Bihari *et al*, 2013).

In conclusion, we described here a case of parvovirus B19 infection resulting in acute viral hepatitis and transient anemia (aplastic crisis). Although this is a rare presentation, parvovirus B19 should be considered as a possible cause in children presented with acute hepatitis and anemia.

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REFERENCES

- Andreesen R, Brugger W, Thomssen C, *et al*. Defective monocyte-to-macrophage maturation in patients with aplastic anemia. *Blood* 1989; 74: 2150-56.
- Barlow SE, the Expert Committee. Expert committee recommendations regarding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. *Pediatrics* 2007; 120 (suppl 4): S164-92.
- Bihari C, Rastogi A, Saxena P, *et al*. Parvovirus B19 associated hepatitis. *Hepat Res Treat* 2013; 2013: 472027.
- Broliden K, Tolfvenstam T, Norbeck O. Clinical aspect of parvovirus b 19 infection. *J Intern Med* 2006; 260: 285-304.
- Brown KE. The expanding range of parvoviruses which infect humans. *Rev Med Virol* 2010; 20: 231-44.

- Brown KE, Anderson SM, Young NS. Erythrocyte P antigen: cellular receptor for B19 parvovirus. *Science* 1993; 262: 114-7.
- Brown KE, Young NS. Parvoviruses and bone marrow failure. *Stem Cells* 1996; 14: 151-63.
- Chongsrisawat V, Yoocharoen P, Theamboonlers A, *et al.* Hepatitis B seroprevalence in Thailand: 12 years after hepatitis B vaccine integration into the national expanded programme on immunization. *Trop Med Int Health* 2006; 11: 1496-502.
- Dwivedi M, Manocha H, Tiwari S, Tripathi G, Dhole TN. Coinfection of parvovirus B19 with other hepatitis viruses leading to fulminant hepatitis of unfavorable outcome in children. *Pediatr Infect Dis J* 2009; 28: 649-50.
- Jain P, Prakash S, Gupta S, *et al.* Prevalence of hepatitis A virus, hepatitis B virus, hepatitis C virus, hepatitis D virus and hepatitis E virus as causes of acute viral hepatitis in North India: a hospital based study. *Indian J Med Microbiol* 2013; 31: 261-5.
- Lugassy G. Chronic pure red cell aplasia associated with parvovirus B19 infection in an immunocompetent patient. *Am J Hematol* 2002; 71: 238-9.
- Mishra B, Malhotra P, Ratho RK, Singh MP, Varma S, Varma N. Human parvovirus B19 in patients with aplastic anemia. *Am J Hematol* 2005; 79: 166-7.
- Morita E, Nakashima A, Asao H, Sato H, Sugamura K. Human parvovirus B19 non-structural protein (NS1) induces cell cycle arrest at G(1) phase. *J Virol* 2003; 77: 2915-21.
- Mustafa MM, McClain KL. Diverse hematologic effects of parvovirus B19 infection. *Pediatr Clin North Am* 1996; 43: 809-21.
- Muta T, Tanaka Y, Takeshita E, *et al.* Recurrence of hepatitis-associated aplastic anemia after a 10-year interval. *Intern Med* 2008; 47: 1733-7.
- Pongpan S. Hepatitis. Annual epidemiological surveillance report 2012. Nonthaburi: Bureau of Epidemiology, Ministry of Public Health, Thailand, 2012. [Cited 2014 May 18]. Available from: <http://www.boe.moph.go.th/Annual/AESR2012/index.html>
- Qian XH, Zhang GC, Jiao XY, *et al.* Aplastic anaemia associated with parvovirus B19 infection. *Arch Dis Child* 2002; 87: 436-7.
- Rauff B, Idrees M, Shah SAR, *et al.* Hepatitis associated aplastic anemia: a review. *J Virol* 2011; 8: 87.
- Rianthavorn P, Fakthongyoo A, Yamsut S, Theamboonlers A, Poovorawan Y. Seroprevalence of Hepatitis A among Thai population residing near Myanmar border. *J Health Popul Nutr* 2011; 29: 174-7.
- Servey JT, Reamy BV, Hodge J. Clinical presentations of parvovirus B19 infection. *Am Fam Physician* 2007; 75: 373-6.
- Simon MA. Simian Parvoviruses: biology and implications for research. *Comp Med* 2008; 58: 47-50.
- Sokal EM, Melchior M, Cornu C, *et al.* Acute parvovirus B19 infection associated with fulminant hepatitis of favourable prognosis in young children. *Lancet* 1998; 352: 1739-41.
- Valentin MN1, Cohen PJ. Pediatric parvovirus B19: spectrum of clinical manifestations. *Cutis* 2013; 92: 179-84.
- Young NS, Brown KE. Mechanisms of disease: parvovirus B19. *N Engl J Med* 2004; 350: 586-97.