Case Report
Parvovirus B19-induced Thrombocytopenia and Anemia in a Child with Fatal Fulminant Hepatic Failure Coinfected with Hepatitis A and E Viruses

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Summary
A 5-year-old male, drowsy, jaundiced child presented with fulminant hepatitis and had HAV and HEV infection. He had hepatic encephalopathy grade 1, fever, pallor, hypotension, crepitations in his right lung base and hepatosplenomegaly with dyspnoea. He had highly raised liver enzymes and hypoalbuminemia (2.8 g/dl) but anemia (hemoglobin of 7.7 g/dl and 5.7 g/dl 2 days later), reticulocytopenia and severe thrombocytopenia (44 × 10^9/l) were unexplained. Parvovirus B19-specific IgM antibodies and B19 DNA were found in the serum of the child. Chest X-ray showed pleural effusion and bronchopneumonia, while blood culture isolated coagulase-negative staphylococci (BACTEC 9120) and he had low oxygen saturation. Hence, he was treated with IV amoxicillin+ clavulanic acid and oxygen inhalation. He had seizures and cardiac arrest but was revived. On the third day his condition worsened and the child died despite intensive care. Hence it is concluded that his anemia and thrombocytopenia were B19 induced and this might have aggravated or caused fulminant hepatitis.

Key words: hepatitis, liver failure, PCR, parvovirus B19.

Introduction
Human parvovirus B19 (B19) is a newly emerging single stranded DNA virus in the family parvoviridae with an increasing spectrum of clinical manifestations [1, 2] including hepatitis which is commonly caused by hepatotropic (hepatitis virus A–E) viruses. Moreover, in a third to half of all children with fulminant hepatitis (FH) no cause has been found [3]; hence infection with B19 remains a possibility. Parvovirus B19 DNA has been found in the liver of patients with fulminant hepatic failure (FHF) associated with bone-marrow aplasia, and in serum of patients with acute, otherwise unexplained, hepatitis [3, 4]. We report here the first fatal case of a child with FH due to multiple infection with hepatitis viruses A and E together with B19 (B19-specific IgM antibodies and B19 DNA by PCR) and who had anemia and thrombocytopenia induced by B19.

Case Report
A 5-year-old male child, resident of Jaunpur (Uttar Pradesh), India was admitted on 3 August 2008 to the Critical care unit of our super specialty tertiary care institute with complaints of high to moderate grade fever associated with poor appetite since last 3 weeks. Yellowish discoloration of eyes and urine were observed 5 days prior to admission. The child was not vaccinated against hepatitis A and B. He was prone to febrile seizures in the past, but there was no family history of similar illness.

The child was drowsy, febrile (101°F), weighed 15 kg and height was 102 cm (corresponding to 5th percentile according to CDC, 2000 standards), had moderate to severe pallor and icterus, heart rate was 110/min and respirator rate was 45/min while his systolic blood pressure was 80 mm Hg. Crepitations were found at the base of right lung. There was hepatosplenomegaly (liver was felt to be 6 cm below the costal margin and was soft to firm; while spleen was 5 cm below the costal margin) and level of consciousness was M4V3E3 on Glasgow coma scale.
Laboratory findings
Hemoglobin was 7.7 g/dl which further decreased to 5.7 g/dl 2 days later with hypochromia and anisocytosis, hematocrit was 36.7% while reticulocyte count was reduced to 0.4%. Total leucocyte count was $22 \times 10^3/\text{l}$ which further increased to $55 \times 10^3/\text{l}$, by 5 August 2008. Platelet count was $44 \times 10^3/\text{l}$, while ESR was 56 mm (Wintrobe method at 1st h). The prothrombin time was raised to 22.4s (control: 11.8s) with hypoalbuminemia (2.8 g/dl on admission which further reduced to 2.0 g/dl by 5 August 2008). The total serum bilirubin was 8.5 mg% while direct bilirubin was 5.2 mg%, ALT and AST were 105 IU/ml and 287 IU/ml on admission which further increased to 217 IU/ml and 1137 IU/ml, respectively. Serum alkaline phosphatase was increased to 906 IU/l. Anti-hepatitis A virus (HAV) IgM and anti-hepatitis E virus (HEV) IgM were positive (by Minividas, Biomerieux and MP diagnostics, Germany kits, respectively) while hepatitis B surface antigen (HBsAg), malarial parasite and Widal tests were negative.

PCR for the detection of parvovirus B19 was positive from serum (DNA extracted by QIA amp Ultra Sens kit, Germany) using primers from VP1 to VP2 common region as described previously [5, 6]. Parvovirus B19-specific IgM was positive by ELISA (IBL Hamburg, Germany). Coagulase negative staphylococci was isolated from blood culture (BACTEC 9120, Becton Dickinson, USA) on admission, which was susceptible to oxacillin, amoxyccillin, vancomycin, amikacin, tetracycline and clindamycin while being resistant to erythromycin and ciprofloxacin.

Clinical diagnosis of acute viral hepatitis, with hepatic encephalopathy grade-1 with moderate to severe anemia, sepsis with severe pneumonia associated with bilateral pleural effusion was made.

Clinical course
The child was started on IV amoxycillin clavulanate, IV fluids and oxygen inhalation. On the second day, he also developed poor air entry and chest X-ray was suggestive of pleural effusion and bronchopneumonia. Ultrasound examination of abdomen on 4 August 2008 showed hepatosplenomegaly bilateral pleural effusion with fluid collection in pelvis. Subsequently respiratory symptoms as well as chest X-rays worsened and he could not maintain oxygen saturation, even by oxygen inhalation. His blood pressure was 80 mm Hg systolic and peripheries turned cold. Patient developed seizures involving left half of body, which was managed by administration of IV diazepam and phenytoin. He was transferred to the postoperative ICU for ventilatory support. His PO$_2$ ranged from 50% to 60%; soon after, the patient had cardiac arrest but was revived by IV dopamine and assisted ventilation. However, patient’s condition worsened further and he died on 6 August 2008.

Discussion
B19 DNA has been found in liver samples from 67% of patients with non-A, -B, -C FHF, 50% of patients with cryptogenic FHF and 15% of control subjects with chronic liver disease [3]. Both Hepatitis A and E cause acute hepatitis and occur commonly in children within the first decade of life.

The pathophysiology of the associated liver disease in B19 infection is unclear but it may be due to direct cytotoxic effects by NS1 protein of B19 on hepatocytes or due to immunological mediation. The cell receptor for B19 is blood group P antigen (tetra-hexose ceramide), which is expressed on surface of erythroid progenitor cells, hepatocytes, myocardial cells, vascular endothelial cells and megakaryoblasts.

We speculate that HAV and HEV individually or together with B19 might have caused the massive liver necrosis and unfavorable course in this patient.

Although dengue fever was suspected in this case because of fever with thrombocytopenia, but he lacked the clinical features besides ELISA for dengue antigen (biorad, USA) as well as IgM antibody capture ELISA (Panbio, Queensland, Australia) were found to be negative.

Parvovirus B19 infection may cause myocarditis [12] and acute heart failure, which remains a rare possibly accounting for cardiac arrest leading to death of the patient.

Furthermore, B19 circulating in the child’s serum were more than $2.4 \times 10^2$ genome equivalents/ml as detected by in-house PCR (sensitivity = $2.4 \times 10^2$ genome equivalents/ml of serum) [6]. Therefore, B19 viremia and presence of anti-B19 IgM antibodies were diagnostic of acute B19 infection causing FH along with anemia and thrombocytopenia. To the best of our knowledge, there is no data on mortality in children due to coinfection of B19 in cases of fulminant viral hepatitis. We had previously reported the first global case of B19-induced acquired pure amegakaryocytic thrombocytopenia in a 9 month old male infant who recovered completely [8] and that B19 is even capable of causing such a severe dysfunction of thrombopoiesis. Long-term longitudinal studies are required to determine parvovirus B19 coinfections in hepatitis.

References