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Hepatitis A and parvovirus B19 infections in an infant with fulminant hepatic failure

Bir süt çocu¤unda fulminan hepatik yetmezlik etyolojisinde hepatit A ve parvovirus B19 enfeksiyonlar›

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Acute viral hepatitis with hepatitis A, B, C, D, and E viruses in the etiology of fulminant hepatic failure either single or in combinations has been described. Parvovirus B19 is also an etiologic agent of acute liver failure and hepatitis-associated aplastic anemia. We present a patient diagnosed with fulminant hepatitis A referred for liver transplantation. Parvovirus B19 superinfection was detected when the patient developed anemia during the course of the disease. We discuss possible roles of both viruses in fulminant hepatitis and pure red cell aplasia.

Key words: Fulminant liver failure, children, hepatitis A, Parvovirus B19

Akut viral hepatik etkenlerinden hepatit A, B, C, D, E virüslerinin tek başlarına veya birlikte fulminan hepatik yetmezliğe neden olduğu bilinmektedir. Parvovirus B19, akut karaciğer yetmezliği ve aplastik anemi ile birlikte görülen akut hepatitlerin etkeni olarak tanımlanmıştır. Burada fulminan hepatit A tanısıyla karaciğer transplantasyonu için gönderilen bir çocukta hastalık seyrinde gelişen anemi nedeni olarak Parvovirus B19 super enfeksiyonu sunuldu. Her iki virusun da fulminan hepatit ve eritroid hipoplazi gelişimindeki rolleri tartışıldı.

Anahtar kelimeler: Fulminan karaci¤er yetmezli¤i, çocuk, hepatit A, Parvovirus B19

INTRODUCTION

Acute viral hepatitis with hepatitis A, B, C, D, and E viruses in the etiology of fulminant hepatic failure either single or in combinations has been described (1). Fulminant hepatic failure (FHF), which occurs in less than 1% of the cases, is a severe complication of hepatitis A virus (HAV) infection. It is a frequent cause of FHF among Turkish children (2). Parvovirus B19 (PVB19), the agent that causes erythema infectiosum (fifth disease), has been suggested as one of the causes of acute non-A, non-E hepatitis (3). It was also proposed as an etiologic agent of FHF-associated aplastic anemia (4) and hepatitis-associated aplastic anemia (5). It can be transmitted through respiratory secretions, transplacentally, and by transfusion of blood or blood products (6). This virus infects the erythroid progenitor cells, stops erythropoiesis, and causes bone marrow failure in immunocompromised patients. Its DNA has been found in the liver of patients with FHF associated with bone marrow aplasia and in the serum of young children with fulminant hepatitis of unknown etiology (4).

We present a patient diagnosed with fulminant hepatitis A referred to our hospital for liver transplantation. Parvovirus B19 infection was detected when the patient developed anemia during the course of the disease.

CASE REPORT

A two-year-old previously healthy male infant diagnosed with hepatitis A was referred to our hospital for liver transplantation due to worsening of blood coagulation parameters, progressive increase in bilirubin levels and encephalopathy. The interval between the onset of jaundice and encephalopathy was 60 days. He was the first child of nonconsanguineous, healthy parents. There was no

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history of previous liver disease, exposure to toxic agents or intake of any herbal medicine.

His weight was 14.5 kg (90th percentile) and height 89 cm (75th percentile). On physical examination he was deeply jaundiced, his liver and spleen were both 2 cm palpable at midclavicular lines. He was in grade II hepatic encephalopathy with inconsolable crying and agitation. Examinations of other systems were all normal.

Laboratory tests on admission were as follows: hemoglobin (Hb) 11.3 g/dl, white blood cell (WBC) count 8.6x10^{9}/L, platelet count 465x10^{9}/L, reticulocyte count 1.81%, C-reactive protein (CRP) 15 mg/L, sedimentation rate 10 mm/h, glucose 63 mg/dl, aspartate aminotransferase (AST) 582 IU/L, alanine aminotransferase (ALT) 614 IU/L, gamma glutamyl transpeptidase (GGT) 50 IU/L, alkaline phosphatase 714 IU/L, total bilirubin 25.9 mg/dl, direct bilirubin 17.4 mg/dl, total protein 5.72 g/dl, albumin 2.88 g/dl, cholesterol 73 mg/dl (N: 110-200), NH3 100 µmol/L (N: 14.7-55.3), PT 29.7 sc, INR 2.88, aPTT 46.4 sc, fibrinogen 115 mg/dl (N: 200-400) and F-V level 20% (N: 60-150%). Serology for human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV) was negative. Anti-HAV IgM and anti-HAV IgG were positive. Serum copper and ceruloplasmin levels were normal. Anti nuclear antibody, anti-dsDNA, anti-LKM-1, and anti-SMA were all negative. Metabolic tests including tandem mass spectrometry and urine organic acids were compatible with severe liver failure.

Four days after admission, the Hb level decreased to 5.83 g/dl. He had no hemorrhage, fever, rash, lymphadenopathy or arthralgia. Haptoglobin and glucose-6-phosphate-dehydrogenase enzyme level was normal and direct Coombs' test was negative. Osmotic fragility and Hb electrophoresis could not be performed due to previous blood transfusions at the referral hospital. At this time PVB19 IgM antibody was found positive. Erythroid hypoplasia compatible with pure red cell hypoplasia was demonstrated by bone marrow examination.

The histologic examination of liver biopsy specimen was reported as massive hepatic necrosis. The patient was registered on the urgent liver transplantation waiting list. He was supported with plasmapheresis five times for bridging to liver transplantation. He died on the 8th day of hospitalization due to multiple organ failure. No suitable liver donor was available for him during this time.

DISCUSSION

In this case, fulminant hepatitis seems to have been caused by hepatitis A infection with PVB19 infection superimposed on it. Experimental intranasal PVB19 infection in adult volunteers confirmed that viremia appears from 7 to 10 days after infection and continues for another seven days, indicating that the PVB19 infection in this case may have occurred following hepatitis A infection.

Patients with fulminant hepatitis A are known to have a spontaneous better prognosis than those with FHF of other causes, as up to 70% of them may survive without liver transplantation (7). Poor prognosis of fulminant hepatitis in this patient could be related to PVB19 super-infection on hepatitis A infection. Previous reports have described co-infection of hepatitis B with PVB19 (8). This co-infection did not increase the severity of the liver disease as determined by the levels of AST, ALT, total and direct bilirubin, and albumin. As far as we know, no reports have detected such a relationship between HAV and PVB19 infection.

The pathophysiology of the associated liver disease in PVB19 infection is not clear. The first hypothesis is based on a direct cytopathic effect and the second on immunological mediation. Hepatic manifestations of PVB19 infection range from abnormal liver function tests to FHF, especially in young children (9). The main distinctive features of PVB19-associated FHF in young children are low bilirubin levels, high ALT and/or AST activity, and favorable outcome with rapid return to normal liver function without orthotopic liver transplantation. Rash, arthropathy and hematologic disturbances did not necessarily accompany FHF (9).

Unfortunately, PVB19 polymerase chain reaction (PCR) from liver tissue was not available in our patient. Nonetheless, in previous studies, PVB19 genome was found in liver tissues of patients with FHF but also in liver tissues from control patients, suggesting that viral genome found in liver tissue may not be specific for acute infection (4, 10). We speculate that HAV by itself or together with PVB19 might have caused the massive liver necrosis and unfavorable course in this patient.

The primary cause of anemia in this patient could be HAV or PVB19. Viral infections have been

shown to induce aplastic anemia, unidentified types of hepatitis viruses being the most common cause of aplastic anemia-associated viral hepatitis. Erythroid hypoplasia and aplastic anemia associated with HAV infection has been reported before (11). Anemia in HAV infection may be related with its direct cytotoxic effect on erythroid progenitors and peripheral destruction of mature red blood cells in the course of disease. PVB19 has also been reported as the possible cause of aplastic anemia, erythroid hypoplasia with maturation arrest, leukopenia, and thrombocytopenia (4, 5, 12).

The sudden fall in the serum Hb in this patient developed two months following the onset of jaundice. Possible mechanism of anemia can be attributed to late effect of HAV infection in this case. A one-month interval between clinical onset of hepatitis A and pure red cell hypoplasia was reported previously (12). Although there was a weak possibility due to the two-month interval between the anemia and HAV infection, hepatitis A could have been the cause of anemia.

Secondly and more probably, the anemia could have been secondary to PVB19 infection acquired during the course of the disease. Our patient had received erythrocyte and fresh-frozen plasma infusions several times before referral to our hospital. Possible contamination of these blood products with PVB19 virus could lead to PVB19 infection and anemia. In fact, it was previously reported that the virus is highly resistant to inactivation by heat and solvent/detergent (13).

Chehal et al. (12) described an adult patient with both HAV and PVB19 infection. This association was complicated by pure red cell aplasia and steroid refractory autoimmune hemolytic anemia. Cyclosporin A therapy resulted in rapid and dramatic improvement in hematologic parameters. We excluded hemolytic anemia with blood tests and bone marrow examination. We are not able to diagnose whether the bone marrow aplasia was due to hepatitis A infection itself or PVB19 infection in our patient.

In conclusion, clinical outcome of HAV and PVB19 co-infection or superinfection has not been defined yet. We could not confirm whether the HAV infection was solely responsible for this patient's FHF; however, this is the first case reporting PVB19 superinfection on fulminant HAV infection. It may be worthwhile to investigate whether their coexistence has a negative effect on liver regeneration in patients with FHF. We believe the recognized clinical spectrum of PVB19 infection continues to expand.

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