Turk J Gastroenterol 2008; 19 (4): 281-283

Adenovirus infection as possible cause of acute liver failure in a healthy child: A case report

Adenovirus infeksiyonu: Sağlıklı bir çocukta akut karaciğer yetmezliğinin muhtemel bir nedeni olabilir: Olgu sunumu

Ferda ÖZBAY HOŞNUT[1], Oğuz CANAN[1], Figen ÖZÇAY[1], Banu BİLEZİKÇİ[2]

Departments of [1]Pediatric Gastroenterology, Hepatology and Nutrition and [2]Pathology, Başkent University Faculty of Medicine, Ankara

Adenoviruses are common viral pathogens in childhood; however, they can cause serious disease in an immunocompromised host. Fulminant hepatitis is a rare complication of adenoviral infection. We report herein a case of fatal fulminant hepatitis possibly caused by adenovirus infection. Although rare, adenovirus infection should be considered in the differential diagnosis of acute liver failure in immunocompetent children.

Key words: Adenovirus, acute liver failure, polymerase chain reaction

Adenoviruslar çocukluk çağında yaygın olarak görülen viral infeksiyonlardır. Fakat, immunsupresif kişilerde ciddi hastalıklara neden olabilirler. Fulminan hepatit, adenoviral infeksiyonun nadir bir komlikasyonudur. Bu yazıda adenovirus infeksiyonuna bağlı olabileceği düşünülen fatal seyreden fulminan hepatitli bir olgu sunulmuştur. Nadir olmasına rağmen immunsupresif olmayan çocuklarda akut karaciğer yetmezliğinde adenovirus infeksiyonları ayırıcı tanıda düşünülmelidir.

Anahtar kelimeler: Adenovirus, akut karaciğer yetmezliği, PCR

INTRODUCTION

Any virus that can cause acute hepatitis may potentially give rise to acute liver failure. Such viruses can be categorized as those that primarily affect the liver, such as hepatitis A to E viruses, and those in which liver involvement may occur as part of disseminated infection, such as Epstein-Barr virus (EBV), cytomegalovirus (CMV), varicella zoster virus, herpes simplex virus, and adenovirus (1).

Adenoviruses, which have been suggested as one of the causes of acute viral hepatitis, are DNA viruses that include 47 distinct serotypes that cause disease in humans (2). They are endemic in children, with 80% of 1-to-5-year-olds having antibody to at least one of the many serotypes. In healthy children, adenoviral infection causes a benign, self-limited illness (2). Symptomatology includes pharyngoconjunctival fever, follicular conjunctivitis, epidemic keratoconjunctivitis, myocarditis, hemorrhagic cystitis and acute diarrhea and invagination. The pathogenesis of invagination was attributed to enlarged intra-abdominal lymph nodes. Adenoviruses were recovered from mesenteric lymph nodes (3). Rarely, more virulent types (particularly type 7) can cause respiratory failure, shock and hepatitis in immunocompetent children (3). However, in immunocompromised patients, adenovirus can cause fulminant or disseminated disease such as colitis, pneumonitis, pancreatitis, nephritis, meningoencephalitis and hepatitis (4). Acute liver failure due to adenovirus is rare, and is described especially in immunocompromised patients, in whom it is usually fatal. (4). Herein, we present a previously healthy child who died due to adenoviral acute liver failure.

CASE REPORT

An 18-month-old boy was admitted to a local hospital with watery diarrhea, vomiting and jaundice for the last three days. After admission, his cons-

Address for correspondence: Ferda ÖZBAY HOŞNUT
Başkent Üniversitesi Ankara Hastanesi Fevzi Çakmak Cad.
10. Sok. No: 45 06490 Bahçelievler, Ankara, Turkey
Phone: + 90 312 212 68 68 / 1314 • Fax: + 90 312 215 75 97
E-mail: ferdaozbay72@yahoo.com

Manuscript received: 29.06.2007 **Accepted:** 22.11.2007

ciousness level gradually deteriorated, and he eventually fell into a grade III coma with abnormal findings in blood coagulation tests, and progressive increase in bilirubin levels. He was diagnosed with acute liver failure and transferred to Başkent University Ankara Hospital for liver transplantation. He had previously been healthy, with normal development, and was the first child of unrelated, healthy parents. There was no history of previous liver disease, exposure to a toxic agent or administration of medications.

On physical examination, his weight was 13 kg (50 percentile) and height 80 cm (50 percentile). He was jaundiced and in grade III hepatic encephalopathy. His abdomen was soft and there was no hepatosplenomegaly or ascites. The remainder of his physical examination was normal.

Laboratory tests on admission were as follows (normal range in parentheses): White blood cell count 23.2x109/L, hemoglobin 7.01 g/dl and platelet count 117 x109/L. His glucose level was 9 mg/dl, aspartate aminotransferase (AST) 149 U/L (0-40), alanine aminotransferase (ALT) 193 U/L (0-41), GGT 27 U/L (18-61), ALP 258 U/L (100-250), total bilirubin 49.99 mg/dl (0-1.2), direct bilirubin 26.71 mg/dl (0-0.3), LDH 1234 U/L (180-430), ammonia 120 µmol/L (14.7-55.3), ferritin 4393 ng/dl (20-200), lactate 5.4 mmol/L (0.7-2.1), PT 36.6 sec (11-15), aPTT 46.5 sec (24-40), INR 3.84 (1-1.2), factor V 20% (60-150), fibrinogen 112 mg/dl (200-400), fibrin degradation products 40 ug/ml (0-5), and D-dimer 9.5 ug/ml (0-0.5). Serum quantitative immunoglobulin levels were all within normal limits. Lymphocyte subset analysis was not compatible with immunodeficiency. The ratio of CD4/CD8 was 4.47.

In order to identify an etiologic agent for his disease, serological examinations were carried out on serum samples obtained at the time of admission. Hepatitis A, B, C, E viruses, CMV, EBV, human immunodeficiency virus (HIV), parvovirus B-19, herpes simplex virus types I-II, toxoplasma and rubella infections were ruled out by the serological assays, while serum adenovirus IgM and IgG antibodies were positive. Blood, stool, and urine cultures were negative for bacterial and fungal pathogens. Widal test for salmonellosis was negative. Stool enteric adenovirus antigen test was positive. Peripheral blood adenovirus polymerase chain reaction (PCR) was positive.

His ceruloplasmin, alpha-1 antitrypsin, antinuclear antibody, liver-kidney microsomal antibody, and anti-smooth muscle antibody tests were all negative. His urine organic acid analysis and tandem mass screening for metabolic diseases did not indicate any disease of inborn errors of metabolism. The abdominal ultrasonography showed proximal jejunal invagination. Supportive therapy including plasmapheresis was given for acute liver failure. However, no liver donor was available and the patient died due to multiple organ failure a few days later.

Postmortem histological examination of his liver specimen revealed massive hepatic necrosis. The liver had lost all hepatocytes; the lobule was populated only by macrophages. Slight condensation of reticulin was present, without fibrosis. On immunostaining, adenovirus antigens were not identified and the cells within the lobule were confirmed as macrophages.

Adenovirus PCR was negative in the paraffin blocks of postmortem-obtained liver tissue.

DISCUSSION

We report the case of a healthy 18-month-old boy who developed acute liver failure possibly due to adenovirus infection. Although most adenovirus infections are self-limited, the virus can be associated with lethal infection in both immunocompromised and healthy children (5). A retrospective review of pediatric adenovirus infections disclosed that 11 (2.5%) out of 440 adenovirus infections were classified as disseminated infections (6). Five of these 11 patients were immunocompetent and the mortality rate in this group was 60%, while it was 83% in immunodeficient cases. Rocholl et al. (5) reported that disseminated adenoviral disease occurred at a younger age in immunocompetent children. They also described a case with fulminant hepatic failure, pancreatitis, encephalopathy and basilar pneumonia due to adenovirus infection. An evaluation for liver transplantation was initiated for their patient; fortunately, the patient responded to the cidofovir treatment and recovered without liver transplantation (5).

Several methods are used to detect adenovirus infection depending on the site and severity of infection. Adenovirus can be shown by immunohistology or characteristic pathologic changes including intranuclear inclusion bodies in biopsy material, isolation of virus by culture or PCR, or demonstration of an increase in antibody titers (3). Isolation of adenovirus from possible infectious sites (urine,

stool, respiratory secretion, and cerebrospinal fluid) is not always successful and because of the limited sensitivity, negative cultures for adenovirus from body fluids do not exclude adenovirus infection. On the other hand, positive viral cultures do not provide evidence of invasive or disseminated disease due to shedding of epithelial cells harboring adenovirus (7).

Onset of hepatic injury in the present case appeared to occur concomitantly or just after the watery diarrhea. Therefore, an infectious disease causing acute liver failure was highly possible. Lack of serologic evidence of other etiologic factors causing viral hepatitis, diarrhea and intestinal invagination led us to search adenovirus in the stool and blood (adenovirus serology and PCR). It is known that the presence of the virus in the stool does not indicate clinical adenovirus infection because these viruses may be excreted chronically and asymptomatically. But, in these instances, discovery of a coincident increase in antibody is helpful in the diagnosis (3). Since there was positive adenovirus IgM and IgG antibody, and positive blood PCR, it was conceivable that our patient had primary adenovirus infection.

The histological examination of his postmortem liver biopsy specimen was reported as massive hepatic necrosis without specific inclusion bodies for adenovirus. However, several authors have commented on the difficulty of confirming the adenoviral infection by histopathology. Flomenberg et al. (8) reported that only three of eight bone marrow patients with positive adenoviral stool cultures had diagnostic viral histopathology. Similarly, Parizhkaya et al. (9) reported only three of 70 small bowel transplant recipients diagnosed with adenovirus enteritis had characteristic epithelial changes in small bowel biopsy. PCR is a very useful method in the detection of adenovirus in biopsy tissues. However, adenovirus PCR tested in the liver tissue was found negative in our patient. This could be secondary to massive hepatic necrosis in our patient and clearance of adenovirus from his necrotic liver. Acute liver failure arises from an imbalance between liver cell death and regeneration. Liver cell death occurs through complex cellular interactions and is mediated by immunological, inflammatory and chemical components. Whether adenovirus infection can trigger immune-mediated acute liver failure must be considered.

In conclusion, we recommend that adenovirus infection should be included in the differential diagnosis of fulminant hepatic failure seen in childhood. Blood PCR test may be more sensitive than liver PCR test in the case of acute liver failure with massive hepatic necrosis.

REFERENCES

1. Williams R, Riordan SM. Acute liver failure: established and putative hepatitis viruses and therapeutic implications. J Gastroenterol Hepatol 2000;15(Suppl):17-25.
2. Mitchell DK, Pickering LK. Gastroenteritis. In: Katz SL, Gershon AA, Hotez PJ, eds. Krugman's infectious diseases of children. 10th ed. St. Louis: Mosby, 1998;116-39.
3. McIntosh K. Adenoviruses. In: Behrman RE, Kliegman RM, Jenson HB, eds. Nelson Textbook of Pediatrics. 16th ed. Philadelphia: WB Saunders Co, 2000;994-5.
4. Hough R, Chetwood A, Sinfield R, et al. Fatal adenovirus hepatitis during standard chemotherapy for childhood acute lymphoblastic leukemia. J Pediatr Hematol Oncol 2005;27:67-72.
5. Rocholl C, Gerber MT, Daly J, et al. Adenoviral infections in children: the impact of rapid diagnosis. Pediatrics 2004; 113:51-5.
6. Munoz FM, Piedra PA, Demler GJ. Disseminated adenovirus disease in immunocompromised and immunocompetent children. Clin Infect Dis 1998;27:1194-200.
7. Seidemann K, Heim A, Pfister ED, et al. Monitoring of adenovirus infection in pediatric transplant recipients by quantitative PCR: report of six cases and review of the literature. Am J Transplant 2004;12:2102-8.
8. Flomenberg P, Babbitt J, Drobyski WR, et al. Increasing incidence of adenovirus disease in bone marrow transplant recipients. J Infect Dis 1994;169:775-81.
9. Parizhskaya M, Walpusk J, Mazariegos G, Jaffe R. Enteric adenovirus infection in pediatric small bowel transplant recipients. Pediatr Dev Pathol 2001;4:122-8.