Acute Renal Failure Complicated EBV Infection in Infancy

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Abstract

Infective mononucleosis is an acute, lymphoproliferative disorder caused by Epstein Barr virus (EBV) seen most commonly in children and young adults. Clinical presentation of the disease is characterized by fever, tonsillitis, lymphadenopathy, hepatosplenomegaly; whereas serological findings of this benign disorder include positive heterophilic antibody formation (transient increase in heterophilic antibodies) and prominence of hematological lymphomonocytosis of more than 10% of atypical lymphocytes. EBV infection is usually asymptomatic in childhood but acute renal failure can be a rare complication of EBV infection during its courses. In most cases, the disease resolves completely. Early recognition of EBV infection and estimation of its complication is important for prognosis of disease.

In light of previous literature, we discuss the case evaluated as EBV infection complicated with acute renal failure in early childhood and results of tubulointerstitial nephritis shown on renal biopsy that was later diagnosed by serological examination as EBV infection.

Keywords: Ebstein barr virus; Acute renal failure; Interstitial nephritis

Introduction

EBV infection affects almost all the systems of the body and therefore has a broad spectrum of clinical outcomes. It was discovered 50 years ago by Epstein, Achong and Barr on microscopic examination of cell cultures obtained from Burkitt’s lymphoma. In 1968, EBV was demonstrated as a causative agent for heterophil-positive infectious mononucleosis. In the 1970’s, it was found in certain tissues of nasopharyngeal carcinoma patients. Finally in 1980’s, a correlation between EBV and oral hairy leukoplakia & non-hodgkin lymphoma has been proved in patients with AIDS [1]. The most common clinical feature seen in adults and adolescents of infectious mononucleosis is a triad of fever, sore throat and lymphadenopathy. Serological tests showing positive heterophilic antibodies and peripheral lymphocytosis with atypical lymphocytes have been determined [2,3]. In infants and early childhood, nonspecific and subclinical symptoms are usually observed [4]. In some cases, primary EBV infection remains silent and atypical clinically until this period. Clinical signs related to almost all affected organs of the body appear in atypical type of infection with EBV. Diagnosis is made by specific serological tests [5,6]. In general, primary EBV infection completely heals in otherwise known healthy cases. However, it can be complicated by renal, cardiac, pulmonary, neurological and hematological complications [5]. Acute renal failure related to acute EBV infection has been demonstrated rarely in literature [7,8]. In light of this literature, we discuss here a case of acute renal failure related to EBV infection in a 13 months old male patient.

Case

A previously healthy 13 month-old male patient was admitted to the hospital presenting with 4 days of fever and rash. Before admission, he had used amoxicillin and clavulanic acid in an appropriate dose for upper respiratory tract infection, but fever didn’t subside and body temperature increased up to 40°C with shivering. He had no complaints other than fatigue. His past history and family history were unremarkable.

On physical examination, he appeared fatigued with body weight 9,750 g (25 p), height 76 cm (25-50 p), axillary temperature 39.8°C, blood pressure 100/60 mm hg, heart rate 130/min and respiratory rate within normal range. Lymphadenopathy and organomegaly were not present.

There were no respiratory, cardiovascular, gastrointestinal and neurological signs but fever, mild hyperemia of the pharynx, a maculopapular rash that blanched under pressure and some petechial rashes on the lower limbs were observed.

On total blood count, haemoglobin 10.4 g/dl, leucocyte count 17,060/mm³ (36.2% neutrophils, 48.4% lymphocytes, 11% atypical lymphocytes) and platelet count was normal (309,000/mm³). Liver function and renal function tests and serum electrolytes were found normal. Due to the presence of persistent fever and rash, viral serological tests for isolation of an etiological agent (TORCH, Parvovirus, EBV VCA IgM, EBV VCA IgG), monospot tests, Rose Bengal tests and tube agglutination tests for Brucella, urine and stool analysis and blood cultures were investigated. On examination, direct stool smear was normal. Urine analysis showed no significant results other than proteinuria+, 7 leucocytes and 2 erythrocytes. For differential diagnosis and exclusion of atypical Kawasaki disease, ECHO was performed and found normal. Monospot tests, Rose-Bengal and tube agglutination tests for Brucella were each negative.

On the 4th day of admission, due to the development of low urine output and bilateral orbital edema, laboratory tests were repeated: leucocyte count: 16,600/mm³, hemoglobin 10 g/dl, platelets 173,000/mm³. Serum electrolytes were as follows: sodium 135 mEq/l,
potassium 7.09 mEq/l, chloride 107 mEq/l, bicarbonate 11.5 mEq/l, urea 181 mg/dl, creatinine 4.1 mg/dl, calcium 7.3 mg/dl, albumin 2.95 g/dl, uric acid 3.11 mg/dl with mild elevation of transaminases (aspartate aminotransferase 170 U/l, alanine aminotransferase 79 U/l). Bilirubin and alkaline phosphatase were at normal level. All types of cultures sent were found sterile.

On abdominal ultrasound, the long axis of the right kidney was measured at 82 mm, and of the left kidney 83 mm, >95th percentile for age. Both kidneys had grade 1-2 parenchymal hypoechogenicity. Sonography showed free collections at various sites including perihepatic peri splenic and lower quadrant of the abdomen, the largest measuring 8 mm.

First attempt for treatment was fluid restriction (urine output + insensible losses), sodium bicarbonate (1 mEq/kg) and calcium gluconate (1 ml/kg). Later, the patient developed oligo-anuria, features of acute renal failure and metabolic acidosis, hence hemodialysis treatment in pediatric intensive care unit (PICU) was applied. Serological testing for EBV VCA IgM, EBV VCA IgG performed at admission was positive. No evidence for acute infection was determined in other serological tests. ASO was negative. C3 complement level was normal. Early examination of renal biopsy material showed intense and mixed tubulointerstitial inflammatory infiltration rich with T cells and histiocytes. Immunofluorescence material showed EBV VCA IgM, IgG, C3, fibrinogen, C19, kappa and lambda were negative. Immunohistochemical studies for CMV, EBV, HSV I/II, parvovirus were also negative.

Due to presence of peripheral atypical lymphocytosis and positive serological tests for EBV, the case was evaluated as acute renal failure related to interstitial nephritis, secondary to atypical EBV infection in early childhood. The patient needed sequential hemodialysis due to acute renal failure and metabolic acidosis; complete recovery of renal functions occurred in after about 1 month.

Discussion

EBV infection usually appears as infectious mononucleosis in adolescents and adults whereas it has asymptomatic and nonspecific symptoms in infants and children [2-4]. We present a case where a 13-month-old infant, who had been under treatment for acute infection, developed acute renal failure.

Infectious mononucleosis, when it has significant clinical features, presents as a triad of fever, lymphadenopathy and pharyngitis in half of patients. Much rarely being atypical, it can be complicated with pneumonia, shock, blood dyscrasias, fulminant hepatitis, encephalitis, carditis, arthritis, uveitis and pancreatitis [1]. These rarely found features make the diagnosis of infectious mononucleosis and its differential diagnosis for Kawasaki disease difficult, especially in the early period. So far, one of the rare complications caused by Infectious mononucleosis is an acute renal failure. Also in our case, atypical features of infectious mononucleosis with development of acute renal failure requiring sudden hemodialysis and diagnosis as EBV infection using serological tests are represented. Typical laboratory findings of infectious mononucleosis are atypical lymphocytosis (>10%) with absolute lymphocytosis, positive heterophilic antibodies and mild-to-moderate elevation of serum aminotransferases. The present case demonstrated 17,060 leucocytes/mm3 with 11% atypical lymphocytes. A heterophilic antibody response is not generated well in children below 10 years of age, which is a well-known reaction also in line with the response in our case.

Serological profiles of EBV antibodies are quite characteristic and are necessary for diagnosis of atypical infections [9]. Also in our case, there were no particular signs of EBV infection and diagnosis is on the basis of serological examination and elevation of both EBV VCA IgM and EBV VCA IgG. It is expected that EBV infection alongside amoxicillin use can cause rash, which was also the case with our patient.

In EBV infection, a true renal parenchymal involvement is very rarely found although abnormalities in urine sediment can be seen in 5-15% of cases [10,11]. Wechsler et al. reported that 17 of 556 cases had abnormalities of urine analysis such as microscopic hematuria and proteinuria without renal parenchymal involvement [12]. Lee and Kjellstrand described 14% with proteinuria and 11% with hematuria in 128 EBV infected cases [13]. In another study, where a series of cases of infectious mononucleosis without clinical findings related to renal illness were studied, swelling in glomerular cells and focal interstitial mononuclear infiltration in renal biopsy was found in 12 of 13 patients [14].

Rhabdomyolysis and hepatic failure are the leading causes of EBV-related acute renal failure [7]. In some cases, isolated tubulointerstitial nephritis, mesangial proliferation and tubular necrosis result in renal failure as well [7,8,13]. Mayer et al examined EBV-associated renal failure cases and found 3 rhabdomyolysis, 2 glomerulonephritis, 1 minimal change disease, 1 hemolytic uremic syndrome and 1 interstitial nephritis relevant acute renal failure from 13 cases with ages ranging from 4 to 18 years old. In the majority of these cases, renal failure had recovered completely within 1 to 2 weeks whereas only one patient had required dialysis. In the case of the patient with interstitial nephritis, the patient required renal transplantation despite treatment with prednisolone [7].

Tubulointerstitial nephritis is an unusual cause of acute renal failure in pediatric patients. Greising et al reported 7% of child patients having tubulointerstitial nephritis among all who went on renal biopsy. In this series, FSGS and interstitial nephritis were detected during renal biopsy in the case of a 15-year-old patient with acute mononucleosis [15]. Ellis et al. linked only 2 cases out of a total of 13 TIN patients between 5-16 years old with to nonspecific viral infections [16]. In our case, acute renal failure is found to emerge due to interstitial nephritis. Although it appeared in early childhood, the patient required hemodialysis as acute renal failure and metabolic acidosis developed and his renal functions recovered completely within 1 month.

Summary, it should be kept in mind that in early childhood, the unexpected and abrupt emergence of acute renal failure features in cases with fever can be caused by EBV as an etiological agent and therefore serological tests should be performed. Renal biopsy done in early periods of the disease can further clarify the diagnosis by determining classical tubular cell infiltration.

References