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The Adult Cambodian Man Came with High Grade Fever and Cholestatic Jaundice

Sombat Treeprasertsuk, M.D., M.Sc.*
Varocha Mahachai, M.D., FACG.**

ABSTRACT

We reported the adult Cambodian man came with high grade fever and cholestatic jaundice for 10 days prior to admission. He also developed acute renal failure and hemolytic anemia with skin rash. The ERCP was done due to cholestatic jaundice with thickening gallbladder which revealed normal biliary tree with mild dilated gall bladder and few gall bladder sludge. There was no intra hepatic duct dilatation, and there was no common bile duet stone. The result of bone marrow study showed hypercellular marrow with reactive thrombocytosis. The other serology test for nonhepatotrophic viral study for hepatitis including CMV., EBV. infection showed positive only for Epstein-Barr virus VCA IgG 1 : 320 with four-fold rising in the paired serum(1 : 2,560). The patient got supportive treatment and his general condition was improved and discharged home within 3 weeks with closely followed up. At 8 weeks after the onset of fever, all the clinical parameters turned to normal level. All the investigations and the serological tests as described supported for the Epstein-Barr viral hepatitis .

Key words : Epstein-Barr, viral hepatitis, fever, cholestatic jaundice

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A 27 years old Cambodian man came to our hospital with high grade fever for 10 days prior to admission. He developed fever and jaundice, nausea and vomiting with loosed watery diarrhea for 5-10 times/day for 5 days. He also had RUQ abdominal pain, not radiated and aggravated by deep palpation. He went to see a physician in Cambodia and was diagnosed as acute gastroenteritis. The initial blood tests in Cambodia showed WBC 7,900 cell/ml., Hb = 15.4 g/dL., Hct. 41.2 %, platelet count 213,000, ESR = 10, ALT/AST 339/282 U/L, anti-Hbs : positive, HbsAg : negative, anti HCV : negative, anti HIV : negative, widal test : 1 : 80, BUN 50.5 mg/dl, creatinine 3 mg/dl. He was admitted at a local hospital and was given intravenous fluid and then was told that he might be infected with hepatitis A infection with acute renal failure. In a few days later, he had progressive jaundice so he was referred for second opinion.

He was previously healthy and denied for DM, hypertension, pulmonary diseases, cardiac disease and kidney diseases. He had history of Penicillin and sulfa allergy with developed papule and skin rash. He so-

* *Gastrointestinal and Liver Unit, Bangkok Hospital, Bangkok 10310, Thailand*
** *Gastroenterology Unit, Chulalongkorn University, Bangkok 10330, Thailand*

cially drinks alcohol and denied tobacco or illicit drugs. He also denied traveling history.

On physical examination (admission day) revealed marked jaundice, looked chronically ill, with high grade fever (Temp. 39.0˚C). His body weight and height were 73.3 kg. and 164 cms., respectively. Skin showed marked jaundice with scattered maculopapular rash on his back. Pinkish palpebral conjunctivae with marked icteric sclerae were seen.

There was neither nasal discharge nor oral thrush. His abdomen showed distended with tender hepatomegaly, smooth surface (liver 2 finger breath below right costal margin) and Murphy's sign is negative. Other systems were within normal limit.

The laboratory and x-ray investigations revealed Hb 10.4 g/dL., Hct. 29.7%, WBC 16,000. (PMN 88.0%, Lymph. 7.0%, Mono. 4.0%, Eos. 1.0%) and platelet count 160,000. Liver function tests showed hypoalbuminemia and mixed cholestasis and hepatocellular damage as shown. (albumin 2.90 g/dL, total/direct bilirubin 48.9/41.3 mg/dl, alkaline phosphatase 509 U/L, AST/ALT 209/155 U/L, HBsAg : negative, anti-HCV: negative)

Electrolyte and renal function showed hypokalemia (sodium 134 mEq/L, potassium 2.5 mEq/L, chloride 88 mEq/L, CO2 24.0 mEq/L., BUN 35.34 mg/dL., creatinine 2.59 mg/dL)

- Other systemic infections such as malarial parasites was also negative

- Stool examination revealed normal with negative for occult

- Ultrasound Upper Abdomen showed fatty liver without mass lesion. Mild hepato-splenomegaly. Gallbladder; mild thickened wall (5 mm thick, possible due to acute hepatitis), moderate distension, no stone. Pancreas; prominent size (17 mm thick at body). Normal CBD, intrahepatic duct, both kidneys. No ascites.

The initial diagnosis was systemic infection with mainly affect to hepatobiliary system.

During hospitalization, he was given I.V. fluid and electrolytes supplement. The urine output was within normal limit and creatinine level turned to normal level in the second week. ERCP was done due to cholestatic jaundice with thickening gallbladder which revealed normal biliary tree with mild dilated gallbladder and few gall bladder sludge. There was no intra hepatic duct dilatation, and there was no common bile duet stone. He had been treated with empirical antibiotics (Imipenam and cilastatin) 500 mg. I.V. every 8 hours. It was stopped after the negative result of hemoculture (6 days later). He also had hemolytic anemia with the result of bone marrow study showed hypercellular marrow with increasing megakaryocytes, and erythroid precursors which suggested for reactive thrombocytosis. His fever and jaundice came down slowly. The other serology test for nonhepatotrophic viral study for hepatitis including CMV., EBV. infection showed positive only for Epstein-Barr virus VCA IgG 1 : 320. The patient got supportive treatment and his general condition was improved and discharged home within 3 weeks with closely followed up. Three weeks later, the serology test for Ebstein-Barr Virus VCA IgG was 1: 2,560 Liver function tests at week 6 after the onset of fever with jaundice showed much better. (total/direct bilirubin 3.8/2.9 mg/dl, albumin 4.05 g/dl, AST/ALT 30/33 U/L) Then, at 8 weeks after the onset of fever, all the clinical parameters turned to normal level.

The clinical manifestation of acute febrile with jaundice and resulted in multiple organ involvement, can occurred in any infectious diseases. However, all the investigations and the serological tests of four fold rising of EBV. titer as described supported for the Epstein-Barr viral hepatitis .

DISCUSSION

Epstein-Barr virus is a ubiquitous virus associated with a variety of different diseases and disorders. About 5.7% of non-hepatotropic viral hepatitis was caused by EBV infection. In Thailand, there was a study showed the detection rate of EBV related hepatitis was found in about 3.2% of acute non A to E hepatitis cases[1-3]. Non-hepatotropic viral hepatitis patients were usually found in winter and spring season. The manifestations of Epstein-Barr virus-associated diseases or disorders within the liver, which involve a broad spectrum of histologic and clinical features, ranging from hepatitis through lymphoproliferative disorders to lymphoma, are presented. Confirmation of infection can be performed using serology to detect the interaction of Epstein-Barr virus with the immune system, and the detection of EBV proteins and use of molecular biologic techniques to identify the presence of EBV RNA, and DNA sequences. In serological tests for EBV, anti-virus capsid antigen (VCA)-IgG antibody and anti-early antigen (EA)-IgG antibody were markedly elevated. Of particular utility are in situ hybridization, Southern blot analysis, and polymerase chain

reaction as diagnostic methods to identify specific RNA or DNA sequences. Epstein-Barr virus-associated diseases and disorders including infectious mononucleosis, post-transplant lymphoproliferative disorders, lymphoma, and AIDS are also reported. Some reports showed the correlation of hepatocellular carcinoma (HCC) and EBV. The study by Li W, *et al* showed positive rates of EBV DNA in liver tissue from 115 HCC patients were 28.2%. The existence of EBV infection suggests that EBV may be involved in the hepatocellular carcinogenesis in China. However, Akhter S, et al studied in 31 cases of non-cirrhotic livers with hepatocellular carcinoma and revealed no detection of EBV[4-6].

For the clinical manifestation, there were many reports of pyrexia, pancytopenia and liver dysfunction as described. Autoimmune hepatitis (AIH) was commonly misdiagnosed. The common primary symptom, disease spectrum and prognosis of EBV infected children were fever (66.8%), cough (14.2%), skin eruption (7.9%), lymphadenopathy (5.3%), eyelid edema (3.2%), pharyngalgia (1.6%), cardiac arrhythmia (1.6%), convulsion (1.6%), arthralgia (1.0%), gross hematuria (0.5%). Most systems and organs were involved in the disease, including liver, spleen, lymph nodes, kidney, heart, lung, bone marrow, brain which made the disease spectrum diverse. The most common disease caused by EBV infection was respiratory tract infection (40.5%), followed by infectious mononucleosis (17.9%), Kawasaki disease (6.3%), idiopathic thrombocytopenic purpura (5.8%), viral myocarditis (2.6%), viral encephalitis (2.6%), hemophagocytic syndrome (1.6%), rheumatoid arthritis (1.0%), acute lymphadenitis (1.0%), facial neuritis (1.0%), Evans syndrome (0.5%), systemic lupus erythematosus (0.5%), subacute necrotizing lymphadenitis (0.5%), non-Hodgkin's lymphoma (0.5%), acute aplastic anemia (0.5%), infantile hepatitis syndrome (0.5%). The prognosis of EBV infection was different due to involvement of different systems and organs[7-12].

Jaundice is uncommon and may reflect either more severe hepatitis or an associated hemolytic anemia. Cholestatic hepatitis due to EBV infection is infrequently reported such as in the case of vanishing bile duct syndrome from chronic EBV infection. In acute hepatic failure caused by primary EBV infection had also been reported in about 16 cases, with an overall mortality of 87% (Figure 1). With orthotopic liver transplantation, followed by low-dose immunosuppression, a pooled gammaglobulin preparation containing anti-EBV antibodies, and anti-viral therapy showed good outcome in some reports[13-17].

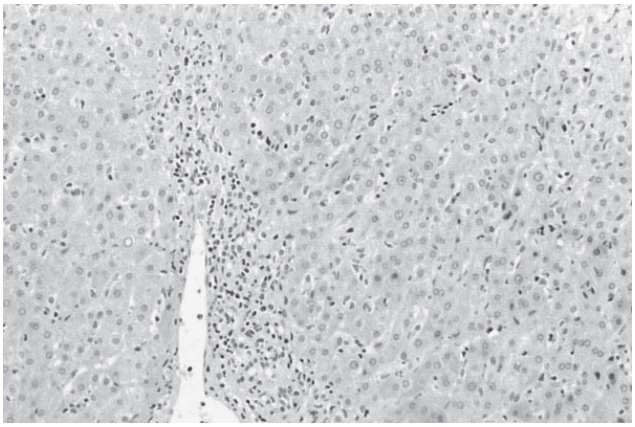

Figure 1 Histological features of acute EBV hepatitis are nonspecific. Mild portal and lobular inflammation is observed (HE). (from: www.yamagiku.co.jp/ pathology/case/case041.htm)

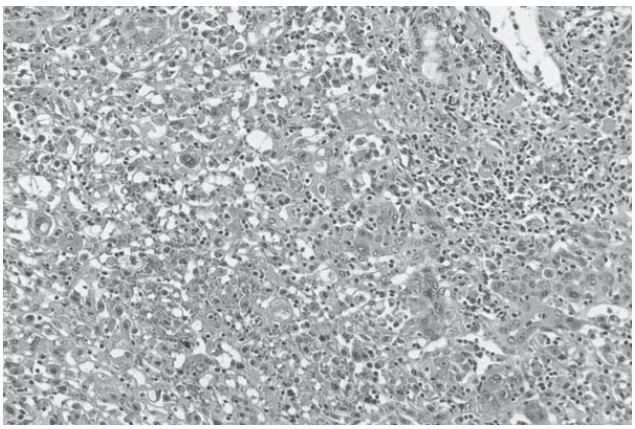

Figure 2 Autopsied liver in case of EBV-related fulminant hepatitis in a 27 year old man (HE). Massive hepatocellular necrosis is seen in the lethal EBV activation. (from: www.yamagiku.co.jp/ pathology/ case/case041.htm)

Abdominal ultrasonography mostly showed splenomegaly. Lymphocytosis and mild leukocytosis were also found. C-reactive protein was only slightly elevated while high alanine aminotransferase (ALT) and a markedly elevated serum alkaline phosphatase level were found. For pathological study in the patient who developed severe hepatitis with prolonged jaundice and confirmed diagnosis of primary infection with EBV by serological study showed spotty necrosis of the liver parenchyma (Figure 2) and infiltration by CD8(+) T

cells which were positive for EBV., but it was negative in hepatocytes[13-15].

In order to determine the factors responsible for the differentiation of cytomegalovirus (CMV) hepatitis and Epstein-Barr virus (EBV) hepatitis in previously healthy adults, the clinical features and laboratory data of both types of hepatitis were compared. In CMV hepatitis showed a tendency of higher detection rate than in EBV hepatitis. CMV hepatitis occurred in significantly older hosts than EBV hepatitis. Lymphadenopathy, cough and sore throat was more common in EBV hepatitis than in CMV hepatitis. The number of peripheral white blood cell count and atypical lymphocytes, and serum AST, ALT, LDH and CRP levels of CMV and EBV hepatitis showed no significant differences[17].

In conclusion, EBV infection should be included in the differential diagnosis of hepatitis of unknown etiology with multiple systems involvement such as hemolysis anemia. T he manifestations of this entity had a broad spectrum and their prognosis depended on their severity. The delay diagnostic may caused a deleterious outcome.

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