

Fatal hepatitis during Epstein-Barr virus reactivation

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Abstract. – Fulminant hepatitis by Epstein-Barr virus is a rare event which is predominantly due to primary infection. We report a rare case of fatal hepatic failure due to Epstein-Barr virus reactivation in a 19-year-old boy who was taking oral steroids. Transaminase peak and the fulminant course of the disease began soon after steroid interruption. Epstein-Barr virus reactivation was diagnosed on the basis of past clinical history of heterophile-positive infectious mononucleosis, a high titer of IgG anti Epstein-Barr viro-capsidic antigen, slight elevation of anti-viro-capsidic IgM, a high titer of anti-EA IgG antibodies and elevated viral load in serum measured by polymerase chain reaction. It is concluded that Epstein-Barr virus should be considered as a possible etiological agent of fulminant hepatitis.

Key Words:

Epstein-Barr virus, Reactivation, Steroids, Fulminant hepatitis.

Introduction

Infectious mononucleosis caused by Epstein-Barr virus (EBV) infection is usually accompanied by a mild, self-limiting hepatic dysfunction. EBV-related liver failure in previously healthy individuals is very rare although it has been reported in immunocompromised patients during primary EBV infection^{1,2}. Cases of fulminant hepatic failure (FHF) induced by primary EBV infection have frequently been described in children affected with the X-linked lymphoproliferative syndrome^{2,3}. We report a very rare case of fulminant hepatitis induced by the reactivation of EBV during immunosuppressive therapy.

Case Report

A 19-year-old male student was admitted to the Department of Infectious Diseases (University of Catania) presenting with fatigue and jaundice. Past clinical history included acute hepatitis A at the age of 7. At the age of 14, infectious mononucleosis had been diagnosed on the basis of prolonged fever, pharyngitis, splenomegaly and positive Paul-Bunnell Davidson test.

Two months before the onset of jaundice, the patient complained of severe arthralgias with joint swelling and fever. A local practitioner diagnosed rheumatoid arthritis on clinical grounds. The patient began therapy with methylprednisolone at a dosage of 40 mg/day orally and a prompt remission of symptoms was achieved. Steroid treatment was scheduled as 40 mg/day for 20 days followed by 20 mg/day for a further 20 days. Thirty days after beginning steroid treatment, the patient developed fatigue, general malaise and became icteric. He did not present fever or sore throat. The liver and spleen were palpable at 6 cm and 4 cm below the costal margin, respectively. No lymphadenopathy was found. Laboratory test results revealed ALT 916 IU/L, total bilirubinaemia 14 mg/dl and prothrombin activity 80%. Total white blood cell count was 9.700 mm³ (neutrophils 38%, lymphocytes 32%, monocytes 30%) and platelets were 108.000/mm³. Serum immunoglobulins were normal. Rheumatoid factor was negative. CD4+ T cell count was 887/mm³ and CD8+ count was 1416/mm³. Abdominal ultrasound scan showed mild hepatosplenomegaly with no evident focal lesions. Serum HbsAg, anti-Hbc IgM and anti-HCV antibody were negative. Anti-Cytomegalovirus; anti Coxsachie

virus A and B and anti-Toxoplasma IgG and IgM antibodies were also negative. Serum HCV RNA was negative as determined by polymerase chain reaction (PCR). HIV 1 serology was negative. Ceruloplasmin was normal and non-organ specific serum autoantibodies were negative. Bone marrow aspirate showed hypercellularity with an increase in atypical lymphoid cells, but with no evidence of histiocytic hyperplasia or prominent haemophagocytosis. The titre of IgG anti-EBV viral capsid antigen (VCA) antibodies was 1/2560; IgM anti-EBV VCA and IgG antibodies against early antigen (EBV-EA) were positive at a titre of 1/320. Finally, EBV DNA was found both in unfractionated whole blood and in serum using both qualitative BamHI-W-repeat PCR and quantitative competitive PCR (viral load: 200,000 copies/ml). The day after admission, methylprednisolone assumption was interrupted. Three days later, both ALT and bilirubin levels peaked at 4810 U/I and 24 mg/dl, respectively. Prothrombin activity fell below 20%. On day 7 following admission, ALT level decreased to 358 U/I and signs of hepatic encephalopathy appeared. The patient was admitted to the intensive care unit. He received intravenous acyclovir, fresh frozen plasma, omeprazole, lactulose and oral neomycin. On day 10 of hospitalization, encephalopathy increased to grade 3 and the patient died before liver transplant could be performed.

Discussion

Infectious mononucleosis is usually a benign disease. Severe complications such as splenic rupture, encephalitis, myocarditis, pericarditis and hepatitis are seen in fewer than 1% of all cases and fatalities are even rarer⁴. Fulminant hepatitis may represent a common cause of death in different types of EBV-induced disorders: (1) spontaneous fatal infectious mononucleosis, whose clinical features are related to primary EBV infection and characterized either by typical symptoms and signs of infectious mononucleosis or by evidence of haemophagocytosis in bone marrow aspirate^{2,3}; (2) X-linked lymphoproliferative disease which is a familial syndrome mostly involving children with abnormal

serum immunoglobulin levels²; (3) post-transplant lymphoproliferative disorders and non-Hodgkin's lymphoma^{2,3}.

The profile of the case presented does not fit any of the above mentioned conditions. This was a case of fulminant hepatitis in a patient who had no evidence of long-standing immunosuppression and was healthy before initiating corticosteroids. As far as we know, this is the first report of fulminant hepatitis due to the reactivation of latent EBV. Past clinical history of infectious mononucleosis, the high titer of IgG anti-Epstein-Barr viro-capsid antigen, the slight elevation of specific IgM and anti-EA IgG antibodies support the hypothesis of viral reactivation in this case⁵, which is further confirmed by the elevated viral load in serum⁶.

A peculiar clinical characteristic of this case was the absence of signs and symptoms typical of EBV infection such as lymphadenopathy and pharyngitis. Overt hepatitis due to EBV in the absence of other signs of infection is uncommon in young patients, whereas this is more commonly seen in patients older than 40^{2,4}.

The reactivation of EBV was probably induced by high-dose steroid treatment or, less probably however, due to autoimmune arthritis. Autoimmune diseases, immunosuppressive drugs, neoplasms, CMV and HIV-1 have been reported elsewhere as underlying causes of EBV reactivation⁷⁻¹⁰. In particular, steroids are a common cause of EBV reactivation from latency. It remains to be established whether steroids may reactivate EBV directly by promoting viral replication or alternatively by down-regulating the ability of the memory T-cell response to control the latent virus. The immunopathogenic mechanisms responsible for liver damage in EBV infection are as yet not clearly specified. EBV produces no direct cytopathic effects in hepatocytes², although sporadic infection of hepatocytes by EBV has been demonstrated¹¹. EBV infection of T cells has been hypothesized to precipitate autoaggressive cytotoxicity¹². Moreover, a cytotoxic T-cell response against EBV-antigens on infected B cells or hepatocytes has been put forward as being responsible for liver necrosis in a pattern similar to that reported for Hepatitis B virus liver damage². In this case, the sudden withdrawal of steroids could have played a triggering role

by inducing an immunologic rebound directed at EBV-infected cells. Studies of withdrawal from corticosteroids have, in fact, already described episodes of hepatic decompensation or worsening of hepatic histology in patients with acute or chronic viral hepatitis¹³. The present study provides evidence that the use of steroids may favour the reactivation of EBV from a latent status. Finally, EBV should be considered as a possible etiological agent of fulminant hepatitis also in the absence of the typical signs of infectious mononucleosis.

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