ORIGINAL ARTICLE

Infectious mononucleosis (Epstein-Barr virus infection) and chronic hepatitis

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ABSTRACT

Aim To describe a case of an eight-year-old boy with chronic Epstein-Barr virus (EBV) hepatitis with incipient cirrhosis, rarely found in practice.

Methods The diagnosis was based on findings of specific IgG serum antibodies and EBV positive liver biopsy. Other etiologies of hepatitis were excluded: autoimmune hepatitis, viral hepatitis A, B, or C, cytomegalovirus (CMV), herpes simplex virus (HSV), adenovirus infection, toxoplasma infection.

Results A mild form of infectious mononucleosis with acute hepatitis without icterus was found in the boy first time at the age of three. He got sick again in april 2018 with fever, minor loss of appetite and weakness, skin and sclera were anicteric, no enlarged neck lymph nodes. Ultrasonography of the spleen revealed a spleen diameter of 10.7 cm, while the liver was 11.8 cm. Laboratory findings, sedimentation, blood count, C reactive protein (CRP) were all normal. Ten days and a month later an increase of aminotransferase was noticed. The liver biopsy and PCR EBV DNA were performed six months of disease onset. The disease had lasted for about one more year with loss of strength and an increase of aminotransferase with maximum value of 3-4 times higher than normal one. The therapy was supportive.

Conclusion Chronic EBV hepatitis is very rare. In differential diagnosis of hepatitis and unclear febrile conditions, EBV infection should not be forgotten.

Key words: biopsy, differential diagnosis, liver cirrhosis

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INTRODUCTION

Epstein-Barr virus (EBV) is the cause of infectious mononucleosis in about 90% of cases (1). In the countries with lower social and economic standards, primary infection breaks out at an age of life. In developed countries, EBV infection is more common in older children, adolescents and younger adults. Infectious mononucleosis is generally a self-limiting disease with a good prognosis (2). Asymptomatic virus carriers are quite common. More than 90% of adults were infected with this virus, which was demonstrated by serological reactions (3).

Primary infection can also result in lethal outcome. It was described in a case of a boy with X-linked lymphoproliferative disease (Duncan syndrome) with abnormal immune response followed EBV infection, resulting in liver function failure, immunodeficiency, lymphoma, lethal lymphoproliferative disease and bone marrow aplasia (3,4). About 75% of the patients die by the age of 10, and all of them by the age of 40 years (with an exception of bone marrow transplantation) (4).

It is known that 80-90% of patients with EBV infection have moderately increased aminotransferase levels and alkaline phosphatase activity in the serum, which indicates liver lesions. During EBV infection, transaminase are typically elevated less than five-fold compared with the normal levels (5). In cases when there are no clinical signs of liver damage, there is always a characteristic histopathological change (6). In only 5% of cases there is hepatitis accompanied with increased bilirubin values (7). The reticuloendothelial system is usually affected as evidenced by generalized splenomegaly (52% of the patients), hepatomegaly (in about 12%) and lymphadenopathy (8). The values of copper and iron in the serum are not significantly disturbed, unless in the case of severe haemolytic anaemia or hepatitis (6,7).

Besides acute hepatitis during primary infection, there are many clinical syndromes associated with EBV infection that are of interest for a hepatologist, such as post-transplant lymphoproliferative disorders, EBV-driven lymphoproliferative diseases and those directly implicated in the pathogenesis of different tumours; EBV has a disputable role in hepatocellular carcinoma (9).

Chronic EBV-associated hepatitis is suspected in immunocompetent adults with compatible serology, suggestive histology and detection of the viral genome in the liver and/or increase of specific circulating cytotoxic T-lymphocytes (8,9).

The aim of this paper is to present the case of a patient with chronic EBV hepatitis and incipient cirrhosis, rarely found in practice.

PATIENT AND METHODS

Patient and study design

A boy aged 8 years, from an urban area in the central part of the Federation of Bosnia and Herzegovina was presented at the Liver Revitalization Centre Vitez in July 2018. He got sick in April 2018 with fever, minor loss of appetite and weakness. The weight was normal and adequate for his age. He was subfebrile and calm. Skin and sclera were anicteric, no enlarged neck lymph nodes. Ultrasonography of the spleen revealed a spleen diameter of 10.7 cm, and the liver was 11.8 cm. Laboratory findings, sedimentation, blood count, C reactive protein (CRP) were all normal. Aminotransferase level was increased at ten days, as well as a month after check-ups. In a paediatric policlinic he was diagnosed with a viral infection.

Previously, at the age of three (2013), the boy recovered from a mild form of infectious mononucleosis (diagnosis confirmed with Monosticon test) with short-term increase in aminotransferase levels, without icterus; serum aminotransferase levels relapsed to normal after ten days, and stayed normal in the following check-ups (up to two years forward).

Methods

The diagnosis of the current disease was based on the laboratory findings of specific IgG serum antibodies and EBV positive liver biopsy. Other hepatitis etiologies were excluded: autoimmune hepatitis, viral hepatitis A, B, or C, cytomegalovirus (CMV), herpes simplex virus (HSV), adenovirus infection, toxoplasma infection.

A laboratory analysis of the blood was performed in Cantonal Hospital Zenica (Vitros 350, Ortho Clinical Diagnostics, USA). Hepatitis A, B and C serologic tests were done at the Department of Transfusion Medicine of Cantonal Hospital Zenica (Architect i2000SR PLUS, Abbot Diagnostics,

Germany): anti HAV IgM and IgG, HBsAg, anti HBs, anti HBc, anti HBc IgM, HBeAg, anti HBe, and anti HCV (hepatitis E marker not performed due to technical reasons) (Table 1). Additional serological tests (EBV, CMV, HSV, adenovirus, toxoplasma) were performed at the Sarajevo University Clinical Centre, Department of Clinical Microbiology (ELISA, Abbot Diagnostics, Germany). The PCR was done at the Sarajevo University Clinical Centre (Real time PCR, Abbot, Germany). Immunological analysis (AMA-M2, M2 3E, SP-100, SLA/LP, PML, Gp210, LKM-1, LC-1, ANA and ASMA) were performed at the Sarajevo University Clinical Centre, Department of Clinical Immunology (indirect immunofluorescence, immunoblot, Euroimmun, Germany). Liver biopsy (reticulum isomers, Trichrome Masson, Perls, staining for copper and iron, CD38, EBV nuclear antigen 2) were done at the Sarajevo University Clinical Centre, Department of Pathology in October 2018.

RESULTS

On the tenth day of the current disease as well as a month later, the laboratory tests were done (Table 1). Abdominal ultrasound was repeated and it showed that the liver was in appropriate position, of appropriate shape, with longitudinal diameter of 9.9 cm, homogeneous structure of parenchyma; spleen was in appropriate position and shape, longitudinal diameter 11.0 cm, homogeneous structure of parenchyma. Gall bladder was moderately distended with appropriate wall thickness. Intra and extra hepatic gall ducts were not dilated. No free fluid wasnoticed in the abdomen nor in the inferior part of the pelvis. Check-up of echo scans of abdomen six months later showed no pathological changes.

Additional serologic diagnostics was also performed two months later for the current disease. Autoantibodies were not detected. Anti HAV IgM was negative, anti HAV IgG was positive, hepatitis B and C markers were negative. ELISA for CMV and HSV IgM and IgG was negative; EBV IgM was negative, IgG positive; ELISA for adenovirus IgM was negative, IgG positive; both toxoplasma IgM and IgG were negative. The PCR EBV DNA in the serum was negative.

The liver biopsy was performed six months after the disease onset. Microscopic representation of cylindrical samples of liver parenchyma with about 10 portal spaces showed discrete to moderate tiny cellular inflammation infiltration and focal image of "interface" hepatitis; there was also a presence of single eosinophil and neutrophil granulocytes. Immunohistochemical analysis with CD38 marker indicated the presence of small number of plasma cells. Periportal fibrosis was also presented extending through the whole cylinder in some areas and with undetermined end. There was fibrosis surrounding regenerative nodules of hepatocytes in one of the cylinders. Along the edge of a cylinder, there was concentric fibrosis around lager bile duct. Hepatocytes lined in mono and bihepatocyte lines without signs of micro and macro vesicular steatosis. Special Trichrome Masson staining indicated multiplied tissue, focal breakdown in reticular net; PAS stains glycogen and PAD-D were negative; special staining for copper and iron deposits was negative. Immunohistochemi-

Table 1. Laboratory findings of the patient on the 10th day and after one month of the disease

Variable	Normal value	10th day	After one month
White blood cells	3.4-9.7 103 uL	9.50	10.90
Red blood cells	4.34-5.72 106 uL	4.71	4.59
Haemoglobin	13.8-17.5 g/dL	155.00	125.00
Platelets	154-424 103 uL	301.00	224.00
Total bilirubin	5-21 umol/L	6.00	8.00
Aspartate aminotransferase (AST)	15-37 U/L	94.00	95.00
Alanine aminotransferase (ALT)	14-63 U/L	160.00	227.00
Gamma-glutamyl transferase (GGT)	25-85 U/L	112.00	158.00
Alkaline phosphatase (ALP)	30-120 U/L	436.00	450.00
Lactate dehydrogenase (LDH)	0-248 U/L	250.00	280.00
Total proteins	62-82 g/L		76.00
Albumins	35-50 g/L		39.00
Globulins	27-35 g/L		37.00
α1 globulins	0.02-0.04 g/L		0.04
α2 globulins	0.07-0.10 g/L		0.13
β globulins	0.9-0.13 g/L		0.16
γ globulins	0.14-0.20 g/L		0.16
Anti HAV IgM	<0.8 negative, >1.2 positive		negative
Anti HAV IgG	<1 negative, >1 positive		positive
HBsAg	<0.85 negative, >1 positive		negative
Anti HBs	normal/N <10		negative
Anti HBc	<1 negative, >1 positive		negative
Anti HBc IgM	<1 negative, >1 positive		negative
HBeAg	<1 negative, >1 positive		negative
Anti HBe	<1 negative, >1 positive		negative
Anti HCV	<0.80 negative, >1 positive		negative

cal analysis with EBV marker indicated focal positivity among lymphocytes in portal spaces. Morphological image suggested hepatitis and incipient cirrhosis.

The disease lasted for about one year with periodical minor loss of appetite and weakness and an increase of aminotransferase level, with the maximum value 3-4 times higher than normal. The therapy of the disease was supportive. There was no EBV disease outbreak noticed.

DISCUSSION

Chronic active EBV infection is rare disorder in which patients are not capable to control viral infection. Out of 100 patients with acute infectious mononucleosis, which was monitored for two years at a clinic in Novi Sad, Serbia, no patient developed chronic form of the disease (10). Because individual cases do not fulfil the diagnostic criteria initially proposed by Straus (11), Kimura and colleagues modified the diagnostic criteria for chronic active EBV infection: illness ≥3-month duration and elevated level of EBV DNA in full blood (12), not in the serum that was done in our patients.

Chronic active Epstein-Barr virus infection presents with chronic or recurrent infectious mononucleosis-like symptoms, such as low-grade fever, liver dysfunction, lymphadenopathy, and hepatosplenomegaly (10). Immunological methods are useful for the diagnosis of viral infections. However, patients do not necessarily have high titer of EBV specific antibodies (13). Antibodies IgM to EB capsid antigen (EBVCA) are evident in 75% of patients within first ten days of primary infection and they completely disappear within two-three months. Antibodies IgG to EB nuclear antigen (EBNA) show up in 4-8 weeks from the beginning of the disease and remain for a lifetime, thus in the first analysis they tend to mostly be negative (14). Our patient was EBV IgG positive.

Chronic EBV hepatitis with initial cirrhosis was shown by the liver biopsies in our patient. In some cases, hepatitis is followed by the ascites break out as well as with described occurrence of autoimmune hepatitis following EBV infection (9,10,15). Reportedly, in seven of 68 liver biopsies of patients with liver disease of unknown etiology, EBV genome demonstrated in the tissue indicated a possible role of EBV in the induction of hepatitis, or a trapping of infected lymphocytes within the liver. In a control group of 20 EBV-seropositive patients with steatohepatitis, EBV-DNA PCR of the liver tissue was negative (16).

The clinical course of chronic active EBV patients can be smouldering, progressive, or aggressive (11,14). From 1998 to 2014, 13 patients aged 10-58 years were diagnosed with chronic active EBV infection at Samsung Medical Centre in South Korea: in the median follow-up of 36 months, 54% patients died, 15% had persistent disease, and 17% patients were free of disease (17).

In conclusion, chronic EBV hepatitis is a very rare disease. In differential diagnosis of the liver disease of unknown etiology EBV infection should be born in mind. The Real-time PCR for EBV analysis should be included in the principal diagnostic tests for febrile children. Timely recognition of the disease is important for adequate management of the patient.

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