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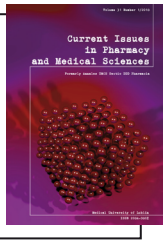

Sever hepatitis induced by Epstein-Barr virus: case series

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ABSTRACT

Epstein-Barr virus (EBV) is a causative agent of infectious mononucleosis syndrome. This infection often resolves over a period of several months without outcomes, but may occasionally be complicated by a great variety of neurologic, hepatic, hematologic and respiratory complications. In the current report, we present the case histories of three patients with acute hepatitis following EBV infection when previously healthy. The patients showed fever, nausea, weakness, as well as yellowing of the skin, and then in the course of examination, sore throat. They were managed supportively and their clinical condition improved. Liver function tests such as ALT, AST, ALP, were undertaken and bilirubin were elevated. The serological tests for EBV infection were consistent with the acute phase of infection. The monospot test was also positive. The patients were managed supportively, and their critical condition was improved.

INTRODUCTION

Epstein-Barr virus (EBV) is a member of the Herpesviridae family of viruses, and it is the cause of heterophile- positive infectious mononucleosis (IM), which is presented by fever, sore throat, atypical lymphocytosis, and lymphadenopathy [1,2]. Most cases of IM are self-limited. Hepatic manifestations, present within 80% of all cases of IM, include self-limited elevation of hepatocellular enzyme levels [3]. The aforementioned elevation is moderate, slightly higher than normal, but EBV causes acute hepatitis rarely [4]. Jaundice is certainly infrequent (5% of the cases) so it is not generally considered a presentation symptom [5].

We describe 3 patients who presented us with hepatitis and jaundice. Their acute EBV infection was confirmed by serology.

CASE 1

A 28-years-old male patient who had weakness, myalgia and fever for a week was admitted to the hospital. After three days, he showed jaundice of the sclera and skin, had nausea and vomiting, and abdominal pain. He had no notable past medical history. Jaundice of sclera, tenderness of right upper quadrant (RUQ) and epigaster, hepatosplenomegaly and temperature 38°C were found on physical examination. Three days after admission, sore throat and exudative pharyngitis occurred. Laboratory studies showed elevated level of aspartate transaminase (AST): 326 U/L, alanine transaminase (ALT): 502 U/L, alkaline phosphatase (ALP): 811 U/L, gamma-glutamyl transpeptidase (GGT): 512 U/L. Total bilirubin was 6.4 mg/dL, conjugated bilirubin was 4.7 mg/dL. The hemogram showed that white blood cell (WBC) count was 6.9×10^3 cell/mm^3 with 62% lymphocytes. Serological tests were negative for hepatitis A, B and C. The prothrombin time was also normal. Wright and Coomb's and also anti-HIV (Ab,), anti-Toxoplasma antibodies (Ab) and anti-Cytomegalovirus antibodies (Ab) were negative, but anti-EBV, VCA, IgM and IgG were positive.

Ultrasonography of abdomen showed increase echogenic on the liver, and the spleen was at 153 mm. Thus, a diagnosis of EBV hepatitis was established based on serology. He was recommended to rest at his house ten days and to come for control again. He returned to clinic after 19 days with laboratory test: AST: 29 U/L, ALT: 21 U/L, ALP: 107 U/L, total bilirubin 0.9 mg/dL, conjugated bilirubin 0.35 mg/dL.

CASE 2

A 19 years old man patient who had weakness, headache, myalgia and fever for a week, was diagnosed with sinusitis, treated with co-amoxiclav and ibuprofen, then recovered

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partly. After three days of symptoms healing, he has a fever, myalgia, nausea or vomiting, abdominal pain and icterus, and with these symptoms, admitted to hospital.

He had no considerable past medical history, although, he had a history of contact with cattle and sheep and with swimming in the river. Were found on physical examination: temperature 38.5°C, jaundice of sclera and skin, left side submandibular lymphadenopathy. He suffered a sore throat and exudative pharyngitis two days after admission.

Laboratory studies showed increased level of AST: 165 U/L, ALT: 176 U/L, ALP 771 U/L, Total bilirubin (≥ 43.03 mg/dL) and conjugated bilirubin (≥ 24.75 mg/dL). The hemogram showed WBC (17.9×103 cell/mm^3 with 64% lymphocytes and 15% atypical lymphocyte). Lactate dehydrogenase was up to 3470. Serological markers for hepatitis A, B, C, leptospirosis, and brucellosis were negative. Prothrombin time was normal. EBV (VCA IgM and IgG) and mono test were positive. Ultrasonography of abdomen showed spleen 171 mm.

The patient suffered anemia associated with hemoglobin decline to 7.2 in admission and was administered a corticosteroid. The patient asked for the following tests: Retic (1.5), Lactate dehydrogenase (LDH) (3470 U/L), Coombs indirect (negative), Glucose-6-Phosphate Dehydrogenase Deficiency (G6PD) (sufficient).

Thus, the diagnosis of EBV hepatitis was established, He was told to rest at his home and come back for control again. He returned to the clinic after 21 days and the then taken with laboratory tests showed: hemoglobine (Hb) (9.4 g/dL), AST: 21U/L, ALT: 19U/L, ALP :100U/L, total bilirubin (1 mg/dL) and conjugated bilirubin were 0.5. He was continually monitored and after one year, hemoglobin returned to 16.9 g/dL.

CASE 3

A 21 years old women who had weakness, myalgia, nausea and vomiting, as well as abdominal pain and fever for the five days prior, was refer to the clinic. Physical examination was febrile and nothing was found. Complete blood count (CBC) and liver function test were requested. Before the test was completed, the patient returned to the clinic with a sore throat and exudative pharyngitis was seen in the pharyngeal examination. Serologic markers were also requested this time. Laboratory studies showed elevated AST: 565 U/L, ALT: 610 U/L, ALP: 538 U/L and total Bilirubin (1.3 mg/dL). In the hemogram, WBC count was 9×10^3 cell/mm^3 with 56% lymphocytes. Prothrombin time was normal. LDH was 662 U/L. Serologic markers were requested for the patient. These included: hepatitis A, B, C, Wright and Coomb's – all were negative. EBV (VCA IgM and IgG) was positive. A diagnosis of EBV hepatitis was thus established. She was recommended to rest at her home and come again for re-control. After than 17 days she returned and was assessed generally good. Laboratory studies showed AST: 32U/L, ALT: 45 U/L, ALP: 163 U/L,WBC (4.1×10^3 cell/mm^3 with 54% lymphocyte).

DISCUSSION

Infectious mononucleosis (IM) is known as an acute clinical presentation of the EBV infection. EBV induces a vast spectrum of illness in humans. Typically, infectious mononucleosis is an acute illness presented clinically by sore throat, fever and lymphadenopathy. Hepatic manifestations consist of a self-limited increase of hepato-cellular enzyme levels. These are present in a significant number of the IM cases.

Elevation is mild, with individual values higher than normal, so that elevation to more than 10 times the upper limit of normal necessitates search for another diagnosis [6]. Fulminant hepatitis is rarely seen in primary EBV infection and suggests an underlying immunodeficiency [7]. The alkaline phosphatase level is elevated in about 60% of the cases. Mild elevation of bilirubin level is distinguished in approximately 40% of all patients, and frank jaundice occurs in only 5%. The characterization of IM with only hepatitis or jaundice and without other symptoms is rare [8]. Cholestatic hepatitis is infrequently reported, while jaundice may result from cholestasis, as well as by the virus-induced hemolysis. Of note, cholestasis can occur during the convalescent phase and bilirubin level change is typically associated with EBV infection [9]. In our patients, AST-ALT reached to 5-20 times the upper limit of normal, and ALP reached to over 600-800 U.L. Moreover, bilirubin level rose to over 40 in two cases (Table1). In a patient with IM, the lymphocyte count constitutes 50% of total WBC. Of this, 10-30% is atypical lymphocytes. First symptoms are weakness, fever, nausea with vomiting, abdominal pain and jaundice. With the mentioned case-studies, we did not think IM at first application, but did so because of the onset of the sore throat, several days later, as well as the lymphocytosis (a case of atypical lymphocytosis). In our patients, peripheral blood smear was 62%, 64% and 50% lymphomonoctosis, respectively, In addition, atypical lymphocytes was 15% in the 2nd case (in other cases it was not checked). Hence, when presented with symptoms of jaundice, peripheral blood smear must be examined.

Table 1. Laboratory characteristics of patients with hepatitis induced by Epstein-Barr virus

	Laboratory findings	First week	Second week	Fourth-fifth week
Case 1	WBC(Cell/mm^3)	5300	6900	6900
	Lymphocyte	50%	62%	40%
	AST (U/L)	216	326	29
	ALT (U/L)	458	502	21
	ALP (U/L)	662	811	107
	Bill T(mg/dL)	4.67	6.4	0.9
	Bill D(mg/dL)	3.2	4.7	0.35
Case 2	WBC (Cell/mm^3)	17900	19000	12400
	Lymphocyte	64%	48%	58%
	AST (U/L)	142	165	21
	ALT (U/L)	130	176	19
	ALP (U/L)	600	771	100
	Bill T (mg/dL)	29.7	43.03	1
	Bill D (mg/dL)	19.3	24.75	
Case 3	WBC (Cell/mm^3)	8000	9000	4100
	Lymphocyte	58.4%	56%	51%
	AST (U/L)	270	565	32
	ALT (U/L)	380	610	45
	ALP (U/L)	425	538	163
	Bill T(mg/dL)	1.3	NL	
	Bill D(mg/dL)	0.3	NL	

Autoimmune hemolytic anemia occurs in some patients with IM. Cold agglutinins, usually of the IgM class, are seen in around 60% of all cases [10], and most but not all cases are mediated by antibodies of this specificity. The hemolysis become clinically definite within the third week of illness and subsides over a several months period [11,12]. Furthermore, corticosteroids may not help recovery in many cases. Still, in one of our patients, hemolytic anemia occur in the second week and corticosteroid was induced by partial regeneration. After a few month, a full recovery was made. Posterior cervical adenopathy is noted in 90% of all IM patients [13], but we did not detect it in ours, so loss of adenopathy must not be the cause of avoiding an IM diagnosis. The diagnosis of EBV infection was done on the basis of usual clinical findings, positive specific and positive heterophile antibody tests. Specific antibody tests of EBV include VCA-IgM, VCA-IgG, diffuse straining component and Epstein-Barr nuclear antigen (EBNA). The detection of EBV VCA-IgM is commonly sufficient for the diagnosis of the acute phase of EBV infection [14]. What is more, the monospot test is a valuable test for heterophile antibody. In our patients, EBV VCA-IgM, VCA-IgG and monospot test were positive. Given overlapping clinical presentations, other potential viral etiologies of hepatitis must be considered where appropriate. These include cytomegalovirus, varicella zoster virus, hepatitis A, B, C, and E, human immunodeficiency virus (HIV), Leptospirosis, syphilis, brucellosis, Wilson disease and Q fever [15]. In our patients, in view of the clinical and laboratory findings, we reached the conclusion of EBV infection.

However, in this report, the patients were healthy people who showed myalgia, weakness and fever, and then had jaundice, nausea or vomiting and abdominal pain leading to cholestatic and sever hepatitis, which improved after an average of 15 to 20 days without medication and only with supportive measures.

CONCLUSION

In differential diagnosis of jaundice and hepatitis, we have to keep in mind EBV-induced hepatitis. The patient may not have typical symptoms and may have only hepatitis clinically even without jaundice. IM should be taken into consideration even if the physical examination result is not parallel, thus, peripheral blood smear and serology must be examined carefully.

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CONFLICT OF INTEREST

All of authors declare no conflict of interest.

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