Case Report

Acute hepatitis: a rare complication of Epstein-Barr virus (EBV) infection

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Abstract

Infectious Mononucleosis (IM), a benign lymphoproliferative disease, is the best known clinical syndrome caused by Epstein-Barr Virus (EBV). It usually resolves over a period of weeks or months without sequelae but may occasionally be complicated by a wide variety of neurologic, hematologic, hepatic, respiratory, and psychological complications. In this report we describe a patient with acute hepatitis following EBV-IM in a previously healthy woman. A 26-year-old woman who presented with fever, generalized weakness, nausea, sore throat, yellowing of skin, and a generalized skin rash was admitted to our clinic. Tonsillar enlargement, pharyngeal erythema, palatal petechiae, lymphadenopathy, and jaundice were noted. Significant atypical lymphocytes (> 10%) were seen on the peripheral blood smear. Liver function tests such as ALT: 303 U/L, AST: 172 U/L, ALP: 193 U/L and total bilirubin: 7.3 mg/dl were elevated. Serological tests for EBV infection were consistent with acute infection (EBV virus capsid antigen was reactive with IgM and IgG antibodies). The Monospot test was also positive. On the seventh day, liver function tests and bilirubin had risen to peak level and platelets were decreased. The patient was managed supportively and her critical condition improved and was finally stabilized. Although the prognosis for IM is very favorable, a variety of acute complications may occur.

Key words: infectious mononucleosis; Epstein-Barr virus; complication; hepatitis

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Introduction

Infectious mononucleosis (IM) is a lymphoproliferative and an infectious disease caused by Epstein-Barr virus (EBV). Approximately 10% of cases are more appropriately termed IM-like illness and may result from primary infection with **c**ytomegalovirus, *Toxoplasma gondii*, human immune deficiency virus (HIV), adenovirus, hepatitis virus infection and possibly rubella virus [1,2]. The incidence in persons younger than 10 years and older than 30 years is less than one case in 1,000 persons per year. However, IM is relatively uncommon in adults, accounting for less than two percent of all adults presenting with sore throat, and incidence of IM does not show consistent seasonal peaks [3].

The infection is spread primarily by saliva, and the incubation period is four to eight weeks. The disease is characterized by a classical triad of fever, exudative tonsillopharyngitis and lymphadenopathy. In addition**,** enanthema, eyelid edema, hepatosplenomegaly and a skin rash may also be observed. The **s**kin rash is usually associated with drug intake, such as beta-lactam antibiotics [4].

The vast majority of patients with IM, especially children, recover uneventfully without any complications, although a wide range of clinical complications of acute EBV-IM have been reported (Table 1) [1-3,5,6]. Hepatic involvement with EBV-IM varies in severity and its frequency varies with age, which is estimated to be 10% in young adults and 30% in the elderly [7]. Although raised serum aminotransferase activities are found in roughly 80% of patients, jaundice occurs in only 5% [8]. EBV infections are often associated with mild hepatocellular hepatitis and can go undetected and resolve spontaneously [9].

Case report

A previously healthy 26-year-old woman who presented with a 10-day history of fever, generalized weakness, nausea, mild sore throat, yellowing and itching of the skin for three days, and a generalized skin rash was admitted to our clinic. There was no history of surgery, blood transfusions, ill contacts, recent travel history, drug ingestions or exposure to mushrooms. There was no family history of liver disease and immunodeficiency. Her history revealed use of amoxicillin-clavulanic acid for seven days for exudative tonsillopharyngitis. Apart from her diagnosis of exudative tonsillopharyngitis, the patient's medical history was unremarkable.

On physical exam, she was in poor general condition and was febrile (39°C). Her blood pressure, pulse and respiratory rate were 110/60mmHg, 100/minute, and 24/minute, respectively. Tonsillar enlargement with membranous exudation, pharyngeal erythema, palatal petechiae, cervical and inguinal lymphadenopathy, scleral jaundice, and mild tenderness in the right upper quadrant were noted. She did not have hepatomegaly and the spleen was palpated 2 cm below the left costal margin. Dermatological examination revealed erosion of the lips with pale erythematous papules and erosion on the face and ears. There was maculopapular rash on the trunk, acral areas, back and legs.

Laboratory findings included a hemoglobin level of 14.1 g/dl (normal range (NR), 12-16 g/dl), total leukocyte count of 28000/mm^3 (58% polymorphonuclear cells, 42% lymphocytes; NR, 4600-10200/mm^3), and platelet count of 297,000 UL (NR, 142,000-424,000 UL). Erythrocyte sedimentation rate was 9 mm/h (NR, 8-15 mm/h) with a C-reactive protein measuring 6 mg/dl (NR, 0-8 mg/dl). Significant atypical lymphocytes (> 10%) were present on blood smear. Serum glucose level, renal function tests and serum electrolyte levels were normal. Liver function tests were elevated: alanine aminotransferase (ALT): 303 U/L (NR, 10-35 U/L), aspartate aminotransferase (AST): 172 U/L (NR, 10-40 U/L), alkaline phosphatase (ALP): 193 U/L (NR, 53-128 U/L), total bilirubin: 7.3 mg/dl (NR, 0.3-1.2 mg/dl), direct bilirubin: 5.9 mg/dl (NR, <0.3 mg/dl). Prothrombin time was also elevated at 17.9 sec (NR, 10-14 sec). The levels of laboratory findings during the follow-up are shown in Table 2. Antinuclear antibody and anti-smooth muscle antibody were negative. Immunologic evaluation consisted of normal serum immunoglobulins, T and B-cell counts, T-cell subsets (CD4+ and CD8+), and complement levels. Serum markers for Hepatitis A (Anti-HAV IgM), Hepatitis B (HBs Ag, Anti-HBc IgM), Hepatitis C (Anti-HCV), and HIV (Anti-HIV) were negative. Hepatitis E (Anti-HEV) measurement was not tested because of unavailability of the test in our laboratory at that time. Anti-toxoplasma IgM, Anti-rubella IgM, Anti-CMV IgM, Anti-HSV IgM were also negative. The Monospot test was positive. Initial serological tests for EBV infection were consistent with acute infection (EBV virus capsid antigen [VCA] was IgM and IgG positive; Epstein-Barr nuclear antigen [EBNA] was negative). Urine analysis revealed no evidence of infection. Abdominal ultrasonography revealed hepatosplenomegaly, minimal ascites and markedly thickened gallbladder wall. Blood, urine, stool and throat cultures were negative for bacterial or viral pathogens.

In view of the clinical and laboratory findings, we reached a conclusion of EBV infection as a cause of the acute hepatitis in this patient. On the seventh day after admission, liver function tests and bilirubin had risen to peak levels (ALT 1141 U/L, AST 1379 U/L, and ALP 297 U/L, gamma-glutamyl transferase 336 U/L, total bilirubin 34.1mg/dl and direct bilirubin 27.6mg/dl) and platelets were decreased to 98,000 UL. The patient was managed supportively with vitamin K, fresh frozen plasma, glucose and aminoacide solution (HepatAmine®). With these treatments, she improved and was discharged on the 42nd day after admission upon complete recovery.

Discussion

Infectious Mononucleosis is known as a benign, usually self-limiting, acute clinical presentation of EBV infection. In developed or industrialized countries such as the United States or European countries, primary EBV infection often affects adolescents or young adults, such as this patient, with no sexual difference [5]. Previous investigations revealed that in poor urban settings or developing countries, 80-100% of children were seropositive by three to six years of age; however, in developed countries, seropositivity often occurs between the ages of 10 and 30 years [5,10,11]. The cause of difference in age distribution of primary EBV infection is unclear. The denseness of population and poor public hygiene status may partly contribute to this difference. EBV infection is transmitted via intimate contact of oropharyngeal secretions. In susceptible patients, EBV invades the epithelial cells of the salivary glands and the white blood cells

known as B cells of the oropharynx, and spreads to the entire lymphoreticular system [7].

The classic triad of IM seen in 80% of the symptomatic cases is characterized by fever, tonsillopharyngitis and lymphadenopathy [1]. When present, the exudate is usually confused with group A streptococcal pharyngitis. A third of patients with EBV carry group A streptococcal organisms; concomitant infection is also common. Because of this overlap, laboratory confirmation is essential to establish exact diagnosis [7]. The other usual clinical findings of IM are hepatomegaly (10-30%) and splenomegaly (50%). Some cases have eyelid edema without renal involvement [1]. Macular, petechial, scarlatiniform, urticarial, or erythema multiforme can be associated with EBV infection in 5% of patients. Of those patients with EBV who receive amoxicillin, 90- to 100% may develop a pruritic maculopapular rash seven to 10 days after administration of the first dose [7]. The rash appears when a suspected case of Streptococcal throat infection is, in fact, a primary EBV infection. In this report, the patient initially had used amoxicillin-clavulanic acid for seven days for exudative tonsillopharyngitis; erythematous papules developed during this therapy.

The diagnosis of EBV-IMN was done on the basis of classic clinical findings, positive specific antibody tests, and positive heterophile antibody tests. Specific antibody tests of EBV include VCA-IgM, VCA-IgG, diffuse straining component and cytoplasmic restricted component of early antigen (EA-D and EA-R), and EBNA. The detection of EBV-VCA-IgM is generally sufficient for the diagnosis of acute EBV-IMN [3]. Recently, real-time polymerase chain reaction (PCR) assays are being used for diagnosing of symptomatic EBV infection and for monitoring the viral load. However, the PCR-test is more sensitive in the first few days of illness, while specific antibody tests may be more sensitive than PCR later during the course of the illness [1]. Furthermore, the expense of the EBV-DNA PCR is the main constraint for its routine use in developing countries. The monospot latex test is a valuable and useful test for heterophile antibody. It is usually elevated approximately four weeks from the beginning of incubation period [12]. On the other hand, laboratory diagnosis of acute IM is also suggested when leukocytosis with an absolute lymphocytosis (> 50% of the total white blood cell count) and at least 10% atypical lymphocytes are seen on peripheral blood smear. The atypical cells are mature T lymphocytes that have been antigenically activated [13]. Mild thrombocytopenia occurs in 25-50% patients during the second and third week of illness. Both hypersplenism and antiplatelet antibody may have contributed to it [5,14]. In our patient, EBV VCA-IgM, VCA-IgG and Monospot test were positive, Leukocytosis with atypical lymphocytes (> 10%). and mild thrombocytopenia were also seen. The comparison of the results of the diagnostic tests between this case and some reported cases can be seen in Table 3 [7,9,15-17].

Given overlapping clinical presentations, other potential viral etiologies of hepatitis are typically considered where appropriate, including cytomegalovirus, varicella zoster virus, herpes simplex virus, hepatitis A, B, C, and E, and HIV. Leptospirosis, syphilis, brucellosis, drug-induced, autoimmune, ischemic, Wilson disease, and Q fever [4,16]. In our patient, in view of the clinical and laboratory findings, we reached a conclusion of EBV infection.

Complications of EBV infection are believed to be immune mediated rather than cytotoxic and many events can occur because of the host response to the EBV infection of the B-cell [6]. As can be seen in Table 1, numerous complications have been reported in association with IM. Severe hepatitis and liver failure have rarely been reported and are mostly related to congenital or acquired immunodeficiency syndromes, including HIV, complement deficiency, X-linked lymphoproliferative disease, or cancer chemotherapy [4, 18]. Lymphocytic infiltration of the liver and proliferation of Kupffer cells lead to mild intrahepatic cholestasis but with maintenance of the lobular architecture and without necrosis [2]. Mild, transient elevations in hepatic transaminases are common during the second to fourth weeks of illness, occurring in 50-80% of cases, with levels that are usually up to four times normal, although the serum AST may reach 1700 U/L and the serum ALT may reach 1000 U/L [19]. Mild jaundice develops in approximately 5% of cases and may result from cholestasis as well as virus-induced hemolysis [2]. While cholestasis can occur during the convalescent phase of any severe form of viral hepatitis, elevated ALP and bilirubin levels are not typically associated with EBV infection. The mechanism for the obstructive component is unknown; it is assumed to be related to a mildly swollen bile duct rather than an infection of the epithelial cells of the bile ducts [7]. Severe hepatitis may be complicated by ascites [20]. In this report; the patient's medical history was unremarkable, ALT-AST reached to over 1000 U/L

and ALP-bilirubin levels were elevated during the illness.

The prognosis for EBV-IM is very favorable, although a variety of acute complications may occur [2]. Acute hepatitis due to EBV is rare [9], and as can be seen in Table 3, most of the patients completely recovered without specific therapy. Our patient also completely recovered when she was discharged without using any antiviral therapy.

Table 1: Acute complications of Epstein-Barr virus infectious mononucleosis (1-3,5,6)

Complications	Frequency
Splenic rupture	Rare
Airway obstruction	<5%
Ampicillin rash	
After administration of ampicillin or amoxicillin	95%
After administration of other β-lactam antibiotics	40-60%
Neurologic complications	1-5%
Encephalitis or meningoencephalitis	
Cerebellitis	
Cranial neuritis	
Transverse myelitis	
Peripheral mononeuritis and polyneuritis	
Autonomic neuropathies	
Guillain-Barre syndrome	
Hematologic complications	
Hemolytic anemia	3%
Aplastic anemia	Rare
Thrombocytopenia	25-50% (early)
Neutropenia	50-80% (early)
Agranulocytosis	Rare
Pancytopenia	Rare
Hepatitis	
Asymptomatic elevated transaminase	50-80%
Jaundice	5%
Lower respiratory tract complications	
Interstial pneumonia	Rare
Pleuritis	Rare
Cardiac complications	
Myocarditis	Rare
Pericarditis	Rare
Rhabdomyolysis	Rare
Psychological complications	
Metamorphopsia	Rare
Depressive disorders	Rare
Psychosis	Rare
Visual, auditory, or gustatory hallucinations	Rare

Table 2: The laboratory findings of the patient

	Admission time	1st week	2cd week	3rd week	4th week	5th week	6th week	3rd month	6th month	1st year
WBCc (4600-10200/mm^3)	28000	31400	14900	9700	9800	7600	6900	8700	9100	8750
Hemoglobin (12-16 g/dl)	14.1	11.5	11.1	11.5	9.4	11.2	11.6	12.1	12.6	13.9
Platelet (142-424 K/ul)	297	98	137	211	247	281	272	301	255	269
ESR (8-15 mm/h)	9	7	12	3	3	2	2	2	5	6
CRP (0-8 mg/dl)	6	11	12	19	8	6	4	5.1	2.9	3.7
ALT (10-35 U/L)	303	1141	658	170	63	58	51	44	36	34
AST (10-40 U/L)	172	1379	899	113	85	101	69	46	41	39
ALP (53-128 U/L)	193	297	269	237	244	241	189	163	151	142
GGT (0-50 U/L)	-	336	276	222	253	188	98	75	51	47
Total bilirubin (0.3-1.2 mg/dl)	7.3	34.1	29.3	21.1	22.7	13.9	10.4	2.1	1.4	1.7
Direct bilirubin (<0.3 mg/dl)	5.9	27.6	23.6	20.3	16.9	11.5	5.8	0.9	0.6	0.8
Protrombin time (10-14 sec)	17.9	24.4	21.3	18.6	16.9	16.1	14.2	12.8	13.1	12.5
LDH (220-450 U/L)	683	1137	877	365	591	332	301	289	258	261

(WBCc: White blood cell count, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ALP: Alkaline phosphatase, GGT: γ-glutamyl transpeptidase, LDH: Lactate dehydrogenase)

Table 3: Some reported cases of EBV-related acute hepatitis in young adults [7,9,15-17]

Age	Sex	Diagnosis of EBV	Treatment	Outcome	Reference
17	M	Monospot test (+)	Steroid	Died 30 days after onset (Renal and pulmonary failure)	Davis et al, 1980
28	M	Atypical lymphocytes (+)	Conservative	Completely recovered	Shizuma T, 2005
		Anti-EBV VCA Ig M and Ig G (+)			
		EBNA Ig G (-)			
19	M	Atypical lymphocytes (+)	Conservative	Completely recovered	Crum NF, 2006
		Monospot test (+)			
		Anti-EBV VCA Ig M (+)			
21	M	Atypical lymphocytes (+)	Conservative	Completely recovered	Crum NF, 2006
		Monospot test (+)			
18	M	Monospot test (+)	Conservative	Completely recovered	Crum NF, 2006
		Anti-EBV VCA Ig M (+)			
22	F	Monospot test (+)	Conservative	Completely recovered	Lawee D, 2007
20	M	Atypical lymphocytes (+)	Conservative	Completely recovered	Kang et al, 2009
		Anti-EBV VCA Ig M and Ig G (+)			
24	F	Atypical lymphocytes (+)	Conservative	Completely recovered	Kang et al, 2009
		Anti-EBV VCA Ig M and Ig G (+)			
		EBNA Ig G (-)			
28	M	Atypical lymphocytes (+)	Conservative	Completely recovered	Kang et al, 2009
		Anti-EBV VCA Ig M and Ig G (+)			
		EBNA Ig G (-)			
26	F	Atypical lymphocytes (+)	Conservative	Completely recovered	Ulug et al (This report)
		Anti-EBV VCA Ig M and Ig G (+)			
		EBNA Ig G (-)			

(VCA: Virus capsid antigen, EBNA: Epstein-Barr nuclear antigen)

Conclusion

In primary care practice, particularly when there is a high level of viral upper-respiratory infections or group A streptococcal pharyngitis in the community, diagnosis of mild EBV infection is difficult if not impossible. Diagnosis requires a high level of suspicion and supporting laboratory data. The exudative pharyngitis from EBV infection is often confused with streptococcal pharyngitis. If treated with penicillin it results in a non-itchy maculoerythematous rash. The rash could be misdiagnosed as allergy to penicillin. The degree of liver involvement associated with EBV infection is varied. Mild self-limited hepatocellular liver disease with a transient elevation of ALT level is common. Cholestatic liver disease is less frequent and is also self-limited. The prognosis for IM is very favorable, although a variety of acute complications may occur. Severe complications are rare, and most of the complications resolve spontaneously without specific therapy.

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