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Isolated Acute Hepatitis Secondary to Epstein-Barr Virus (EBV) Infection: A Case Report

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Abstract:
Epstein-Barr virus (EBV) is a belong to the Herpesviridae family and is generally known to cause infectious mononucleosis which usually manifesting with fever, lymphadenopathy, and sore throat. However, acute hepatitis due to EBV in the absence of the classical syndrome of mononucleosis is an uncommon presentation and the diagnosis may be challenging. This case report describes the clinical course and management of acute hepatitis induced by EBV infection without the classical mononucleosis syndrome.

Introduction:

Infectious mononucleosis caused by EBV is characterized by symptoms such as sore throat, cervical lymphadenopathy, and pharyngitis [1]. More than 90% of people get infected with this virus worldwide [2]. The liver is one of the organs that may be involved in EBV infection, typically causing a mild elevation in liver enzymes that resolves spontaneously [3]. However, acute hepatitis may rarely develop in the setting of infectious mononucleosis and most importantly, it may present without typical clinical manifestations for EBV infection, particularly among older patients [3,4,5,6]. EBV has also been associated with several cases of chronic hepatitis reported in the literature [7]. Therefore, EBV hepatitis needs to be differentiated from other etiologies of acute hepatitis which include drug-induced hepatitis, autoimmune hepatitis, and other viral hepatitis [8,9,10].
EBV has been an uncommon cause of acute hepatitis in the absence of classical mononucleosis syndrome but does pose a significant diagnostic challenge. Here we report the clinical course and management of a young adult patient with acute hepatitis precipitated by EBV infection in the absence of typical mononucleosis syndrome.

Case report:

A 20-year-old medically free male presented to the hospital with a history of 10-days of abdominal pain and intermittent fever which reached up to 40°C. The abdominal pain was mostly located in the right upper quadrant (RUQ) and the epigastric area, described as dull in nature, radiating to the back. This was associated with nausea, dark urine, and putty colored stools. The patient denied any history of rash, diarrhea, vomiting, illicit drug use, recent travel, or contact with infectious cases.

Upon admission, the patient was alert and fully oriented. His vital signs included a blood pressure of 104/72 mmHg, a temperature of 37.2°C, and a heart rate of 120 beats per minute. Physical examination revealed no rash, lymphadenopathy, flapping tremor or signs of pharyngitis. Cardiovascular and respiratory examinations were unremarkable. Mild tenderness was noted on palpation over the RUQ and epigastric region.

Initial laboratory investigations showed normal complete blood count (CBC) values. Liver function tests (LFTs) demonstrated elevated aspartate aminotransferase (AST) at 166 U/L, alanine transaminase (ALT) at 219 U/L (Graph 1), total bilirubin at 4.3 mg/dL, and direct bilirubin at 3.7 mg/dL (Graph 2). The international normalized ratio (INR) was elevated at 1.7. Abdominal ultrasound initially revealed findings indicative with acute hepatitis.

Over the next few days, the patient experienced a persistent high-grade fever ranging from 38.5 to 39 degrees. A follow-up exam revealed hepatosplenomegaly (liver span of 13 cm) and tenderness in the right upper quadrant and epigastric area.Further laboratory workup revealed leukocytosis with a predominant lymphocytic count. An increased prothrombin time and International Normalized Ratio were observed, with the prothrombin time reaching the maximum limit of 36.8 seconds (Table 1). Liver enzymes and conjugated hyperbilirubinemia remained elevated. on the fourth day of admission, inflammatory markers were significant for a positive C-reactive protein (CRP) and an erythrocyte sedimentation rate (ESR) of 18 mm/hr. Ferritin levels were elevated at 1724.73 ng/mL and lactate dehydrogenase (LDH) was 922 U/L. These levels trended downward by the eighth day, with ferritin at 701.91 ng/mL and LDH at 615 U/L. Tests for immunoglobulins (IgG, IgM, IgA) and anti-smooth muscle antibodies were negative as were serologies for brucellosis and hepatitis. Blood cultures were negative. EBV serology was positive for viral capsid antigen (VCA) IgG and IgM while Epstein-Barr nuclear antigen (EBNA) was negative (Table 2). A peripheral blood smear revealed marked absolute lymphocytosis with the presence of atypical lymphocytes.

Neck ultrasound showed multiple enlarged bilateral cervical lymph nodes, seen mainly in upper deep cervical region. Urgent magnetic resonance cholangiopancreatography (MRCP) was performed to exclude cholangitis, revealing abnormal hepatic parenchyma, splenomegaly, and enlarged abdominal lymph nodes (Figure 1). High-resolution CT (HRCT) demonstrated mild right-sided pleural effusion, hepatosplenomegaly, an edematous gallbladder, and nonspecific porta-hepatitis lymphadenopathy.

The patient was managed supportively with lornoxicam three times daily and a cold compress to help control the pyrexia. Additionally, the patient was empirically started on Piperacillin-tazobactam for nine days. Over time, the patient's condition improved; there were no further fever episodes, and his liver enzymes decreased by the seventh day of admission. When evaluated as an outpatient two weeks later, his LFTs were returned to normal ranges.

Discussion:

EBV primarily infects B lymphocytes and epithelial cells, establishing a latent infection that persists for the lifetime of the host. The virus is mainly transmitted through saliva, leading to high prevalence in populations worldwide. Over 90% of adults test positive for past exposure by the time they reach adulthood [10]. EBV is commonly linked to infectious mononucleosis, but it can also lead to liver involvement. Typically, the liver manifestations are mild and characterized by a temporary increase in liver enzymes, which usually resolve spontaneously in most cases [11].

However, EBV-induced hepatitis without the typical mononucleosis syndrome, as seen in the case of our patient is a much rarer presentation especially in immunocompetent patients [4].
The presentation of EBV-induced hepatitis without mononucleosis syndrome has been documented in several case reports, highlighting the variability in clinical presentation and resulting in a diagnostic challenge. For instance, Moniri et al. described a 23-year-old woman with isolated EBV hepatitis who presented with fever, jaundice, and elevated liver enzymes, but without the classic signs of infectious mononucleosis [4]. Similarly, Edoute et al. reported a case of severe cholestatic jaundice in a 60-year-old man caused by EBV infection, with an absence of concurrent pharyngitis or lymphadenopathy [6]. These cases illustrate that EBV can present predominantly as a hepatic disease without the classic signs of mononucleosis syndrome. Similarly, our patient presented with a 10-day history of abdominal pain and intermittent fever, with no history of lymphadenopathy, pharyngitis or sore throat.

Radiological investigations are also essential for ruling out other causes of hepatobiliary disease [11]. In this case, abdominal ultrasound and magnetic resonance cholangiopancreatography (MRCP) were used to exclude biliary obstruction. As common viral hepatitis markers were absent, the investigation pointed towards EBV as the likely cause of hepatitis. The absence of lymphadenopathy, pharyngitis, and other mononucleosis symptoms delayed the consideration of EBV as a causative agent, which is consistent with findings from previous reports that show a delay in diagnosis in such atypical cases [3,4,9].
The diagnosis of EBV hepatitis relies primarily on serological testing to detect specific antibodies against EBV antigens, such as VCA IgM, VCA IgG, and EBNA [9]. In our case, the positive VCA IgG and IgM results and the absence of EBNA confirmed acute EBV infection.
Due to symptom overlap, it is imperative to exclude other potential causes of hepatitis, including hepatitis A, B, C, and E viruses [12-13]. In our case, all the hepatitis virus results came back negative.

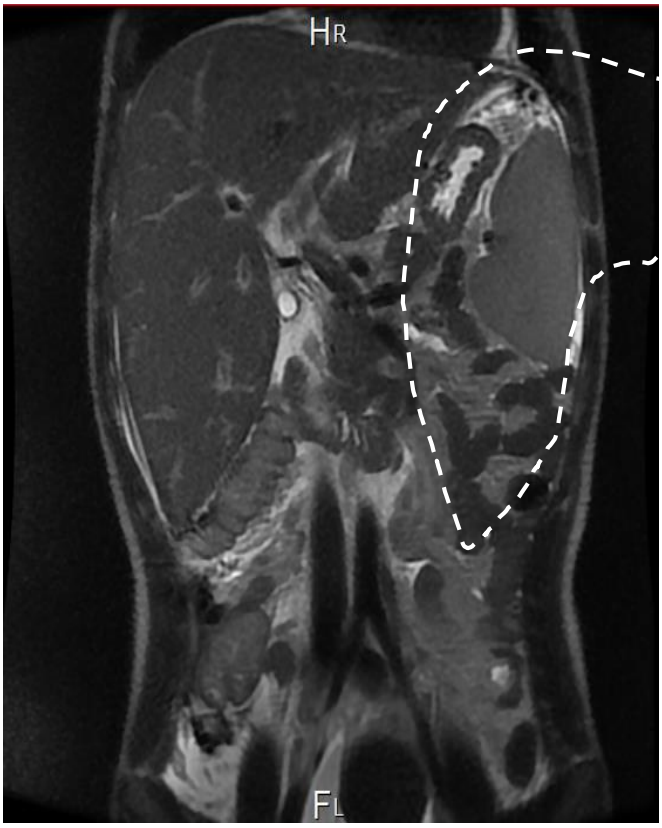
The pathogenesis of EBV-induced hepatitis remains incompletely understood, but it is primarily believed to be immune-mediated. EBV infects B cells, leading to their activation and the subsequent proliferation of cytotoxic T cells, which results in liver injury. This immune response may cause hepatocellular damage, reflected by elevated aminotransferase levels and cholestasis and jaundice in more severe cases [11]. In our case, elevated transaminases, coagulation profile and cholestasis indicated a significant liver involvement.
Some studies have also suggested that EBV may trigger an autoimmune response, which could explain the development of hepatitis in some patients. EBV has been implicated in the pathogenesis of several autoimmune diseases, including autoimmune hepatitis [14-17]. Nevertheless, in this particular case, the absence of autoimmune markers such as antinuclear antibodies (ANA) and anti-smooth muscle antibodies (ASMA) effectively ruled out autoimmune hepatitis.

The management of EBV-induced hepatitis is primarily supportive care, as specific antiviral therapies for EBV are not available for immunocompetent individuals [18]. In our patient, supportive care, including the administration of nonsteroidal anti-inflammatory drugs (NSAIDs), resulted in a gradual improvement in liver function and the resolution of symptoms.
In the majority of cases, EBV hepatitis resolves spontaneously, and the prognosis is generally favorable in immunocompetent patients. However, severe cases, such as those involving acute

liver failure are rare and carry a poor prognosis. Specifically, Zhang et al. reported a case of EBV-associated acute liver failure in a 67-year-old woman who required liver transplantation. Fortunately, our patient did not develop fulminant liver failure, and his liver function tests returned to normal within two weeks of hospital discharge. [19].

Conclusion:

EBV-induced hepatitis without mononucleosis syndrome is a rare but potential cause that can lead to significant diagnostic challenges. In patients presenting with acute hepatitis and no apparent cause, EBV should be considered as a potential etiology, even in the absence of the classic mononucleosis syndrome. This case contributes to the increasing evidence indicating that EBV should be considered in the differential diagnosis of acute hepatitis.



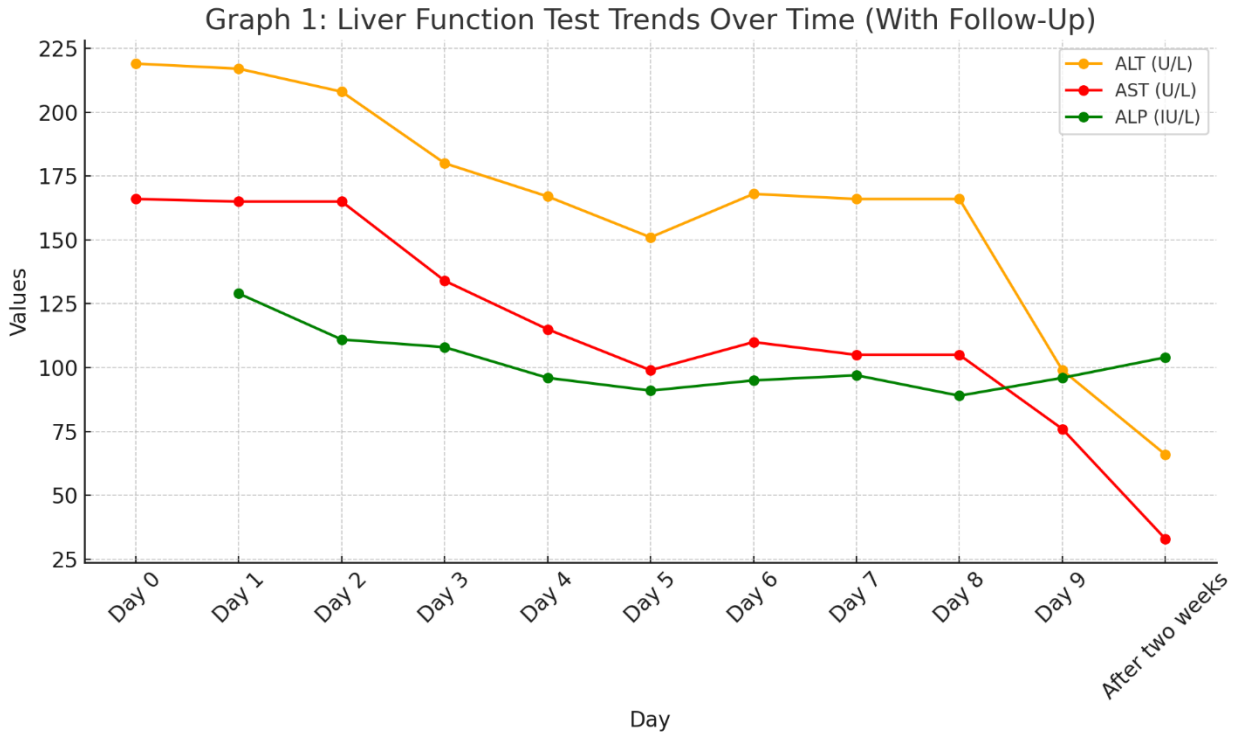
[Picture 1]: Magnetic resonance cholangiopancreatography (MRCP) Showed Abnormal and enlarged hepatic parenchyma (white interrupted line), with splenomegaly (white line) and enlarged abdominal lymph nodes.

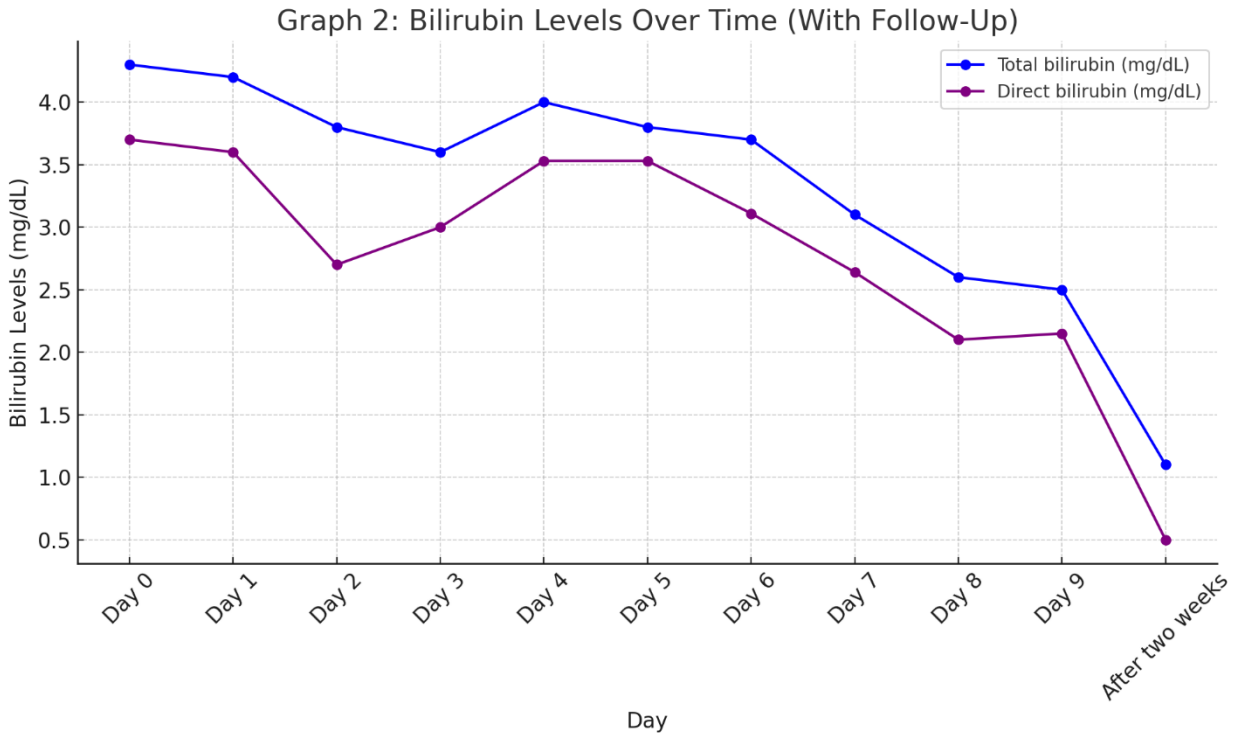
Table 2: Epstein Barr Virus Immunology Test

Lab	Value	Reference Range
Epstein Barr Virus (EBV) VCA IgG	165.00	< 20u/ml = Negative > 20u/ml = Positive
Epstein Barr Virus (EBV) VCA IgM	82.00	< 20 = Negative 20 – 40 = Equivocal > 20 = Positive

Table 1: Coagulation Profile

Lab	Values							Reference Range
	Day 0	Day 1	Day 3	Day 5	Day 7	Day 9	After two weeks follow up	
Prothrombin time (PT)	19.9	20.1	36.8	12.9	12.9	12.9	12.4	9.4 - 12.5 sec
Activated partial thromboplastin time (aPTT)	33.9	37.4	36.2	32.3	32.6	30.9	32.8	25.4 - 38.4 sec
International normalized ratio (INR)	1.7	1.71	3.15	1.09	1.09	1.09	1.1	0.8 - 1.2 sec


Graph 1: Liver Function Test Trends Over Time (With Follow-Up)
ALT (U/L)
AST (U/L)
ALP (IU/L)
Values
225
200
175
150
125
100
75
50
25
Day 0
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Day 7
Day 8
Day 9
After two weeks
Day


Graph 2: Bilirubin Levels Over Time (With Follow-Up)
Total bilirubin (mg/dL)
Direct bilirubin (mg/dL)
Bilirubin Levels (mg/dL)
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Day 0
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Day 7
Day 8
Day 9
After two weeks
Day

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