

Epstein-Barr Virus: An Unusual Cause of Cholestatic Hepatitis in Older Adults

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Epstein-Barr virus (EBV) frequently causes acute infection or infectious mononucleosis (IM) in the adolescent population. Hepatic involvement in these cases is not uncommon and typically is accompanied by elevations in serum aminotransaminases and alkaline phosphatase (AP). In the older adult population, acute EBV infection is a rare occurrence and may present with atypical signs and symptoms, making the diagnosis an elusive one. We report two cases of older adult patients with acute EBV infection, cholestatic hepatitis, and neurologic symptoms.

Case Reports

Case #1

A 73-year-old woman with a history of paroxysmal supraventricular tachycardia, hypertension, partial sigmoidectomy post-colon cancer, and peripheral neuropathy of the lower extremities presented to a local hospital with confusion and fever of 1 day's duration. She complained of chills, fatigue, diffuse myalgias, lethargy, and increasing somnolence. She had recently visited her 3- and 4-year-old grandchildren, but they had not suffered from any recent infectious illnesses. Physical examination revealed a somnolent but arousable patient with a temperature of 103° F, tachycardia of 120 bpm, and a normal blood pressure. The patient displayed occasional myoclonic jerking of all 4 extremities. No other focal physical examination findings were noted.

Subsequently, the patient was admitted to the hospital, and an extensive evaluation was started to find the cause of the fever. Blood tests revealed a white blood cell (WBC) count of 6,100/ μ L (with a differential count showing 61% neutrophils, 5% bands, 24% lymphocytes,

7% monocytes, and 1% reactive lymphocytes), hemoglobin of 12.4 g/dL, and platelets of 167,000/ μ L. Her C-reactive protein was elevated at 113 mg/dL. Liver chemistry tests showed a total bilirubin of 0.4 mg/dL, AP of 73 IU/L, aspartate aminotransferase (AST) of 66 IU/L, alanine aminotransferase (ALT) of 52 IU/L, and gamma-glutamyl transpeptidase (GGT) of 499 IU/L (Table 1). Serologies for hepatitis A, B, and C and heterophil antibody were all nonreactive. Blood cultures were negative, as were titers for antinuclear antigen antibody (ANA) and urine histoplasma antigen.

The patient then underwent a chest radiograph, which was normal, and a right upper quadrant ultrasound, which revealed mild heterogeneity of the liver echotexture and cholelithiasis with no evidence for cholecystitis. Cranial computed tomography (CT) scan, transthoracic echocardiogram, and gallium scan were all nondiagnostic. A lumbar puncture was performed, and the cerebrospinal fluid (CSF) revealed a glucose level of 65 mg/dL, protein of 41 mg/dL, and 1 red blood cell (RBC) and 1 WBC per high power field (HPF). Further evaluation of the CSF found no evidence of bacterial infection, cryptococcal antigen, herpes simplex virus, or enteroviruses. The patient was empirically treated with intravenous ceftriaxone and doxycycline, but her mental status and temperature curve continued to fluctuate. On the ninth day of her hospital stay, her serum bilirubin and AP peaked at 2.2 mg/dL and 560 U/L, respectively. The patient was subsequently transferred to our institution for further evaluation and management.

Following her transfer, a repeat lumbar puncture was performed, and the CSF showed a glucose of 65 mg/dL and protein of 45 mg/dL, and 1 RBC and 1 WBC per HPF. The EBV viral capsid antibody (VCA) immunoglobulin M (IgM) titer was elevated at greater than 640. EBV early antigen (EA) and nuclear antigen antibodies were undetectable. EBV DNA by polymerase chain reaction (PCR) was positive both in the blood and CSF. Antibiotics were discontinued, and the patient's clinical symptoms gradually improved over the next several days. Her

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Table 1. Liver Chemistry Tests for Case #1

	Baseline	Day 1	Day 4	Day 10	Day 12	Day 15	Day 37	Day 76
Total bilirubin (0.0–1.0 mg/dL)	0.3	0.4	0.4	2.2	2.2	1.2	0.4	0.3
Alkaline phosphatase (50–136 U/L)	76	73	132	560	481	458	161	111
ALT (25–73 U/L)	ND	52	50	77	57	60	43	23
AST (11–37 U/L)	30	66	52	81	50	62	32	25

ALT = serum alanine aminotransaminase; AST = serum aspartate aminotransaminase; ND = Not drawn.

Table 2. Liver Chemistry Tests for Case #2

	Baseline	Day 1	Day 4	Day 5	Day 8	Day 15	Day 23	Day 51
Total bilirubin (0.0–1.0 mg/dL)	0.4	0.9	1.9	1.9	0.8	0.7	0.4	0.5
Alkaline phosphatase (50–136 U/L)	74	503	742	912	850	404	169	80
ALT (25–73 U/L)	ND	259	339	400	224	61	27	19
AST (11–37 U/L)	23	313	357	388	115	38	31	22

ALT = serum alanine aminotransaminase; AST = serum aspartate aminotransaminase; ND = Not drawn.

liver chemistry tests normalized over the following several months.

Case #2

A 59-year-old female with a history of chronic urticaria presented with 1 week of headaches, malaise, myalgias, generalized anxiety, and insomnia. Her symptoms tended to wax and wane, and were associated with occasional fevers. On physical examination, the patient was afebrile, awake, alert, and oriented. Her speech was slow but not dysarthric. No focal findings were noted on the remainder of the physical examination.

Her blood tests showed a WBC count of 5,200/ μ L (with a differential count of 45% neutrophils, 24% bands, 22% lymphocytes, 6% monocytes, and 3% reactive lymphocytes), as well as normal hemoglobin and platelet counts. Her serum sodium measured 124 mEq/L. Her liver chemistry tests revealed a total bilirubin of 0.9 mg/dL, AP of 509 U/L, AST of 313 U/L, and ALT of 259 U/L. By the fifth day of hospitalization, these levels had risen to a bilirubin of 1.9 mg/dL, AP of 912 U/L, AST of 388 U/L, ALT of 400 U/L (Table 2). Erythrocyte sedimentation rate was 51 mm/hr. Coagulation parameters and ammonia level were normal, and serologies for hepatitis A, B, and C were nonreactive.

An abdominal ultrasound revealed no evidence of organomegaly, biliary pathology, or focal masses. Other

tests included a normal thyroid-stimulating hormone, serum creatinine kinase, ANA titer, and malarial smear. A magnetic resonance image (MRI) of the brain and an electroencephalogram were nondiagnostic. EBV serologies showed EBV VCA IgM greater than 640, EBV VCA immunoglobulin G (IgG) greater than 320, and EBV EA antibody less than 10. A diagnosis of acute EBV infection was made, and the patient's hyponatremia was attributed to the EBV-related syndrome-inappropriate antidiuretic hormone (SIADH).

While still at the hospital, the patient complained of worsening lower extremity pain. She had developed bilaterally diminished ankle and triceps reflexes, as well as a diminished right patellar reflex. Dorsiflexion was weak in her left foot, but the remainder of her neurologic examination was normal. MRIs of the brain and spine were repeated but remained normal. A subsequent lumbar puncture showed a CSF WBC count of 52 per HPF, with a lymphocyte predominance, glucose of 59 mg/dL, and protein of 110 mg/dL. Gram stain and culture were negative, and no oligoclonal bands were detected. Herpes simplex virus DNA by PCR was not detected in the CSF, although EBV DNA by PCR was positive. Results of a nerve conduction study were consistent with Guillain-Barre syndrome. The patient was subsequently treated with intravenous immunoglobulin for 5 days. A single course of methylpred-

nisolone was started but discontinued due to agitation. The patient's symptoms improved over several weeks, and her liver chemistry tests returned to normal within a month.

Discussion

Epstein-Barr virus is a member of the Herpesviridae family and consists of a linear, double-stranded DNA core surrounded by a nucleocapsid and viral envelope. Epstein-Barr virus infection occurs worldwide and most commonly arises in early childhood, with a second peak occurring during late adolescence. By adulthood, more than 90% of individuals have developed antibodies to the virus; only 3–10% of adults over the age of 60 remain susceptible to primary EBV infection.¹ Retrospective epidemiologic studies have reported the incidence of IM to be 345–671 per 100,000 individuals aged 15–19 per year. It is less common in individuals over the age of 34; the incidence rate is 2–4 per 100,000 individuals per year.² Most early childhood infections are asymptomatic, but symptoms are present in 20–70% of infected teenagers.³ Geographic and socioeconomic factors also account for some of the variation in disease expression, with asymptomatic cases in infants and young children more common in the developing world and symptomatic cases in adolescents more widespread in developed countries.⁴

Epstein-Barr virus typically spreads via oral secretions. EBV infects the epithelium of the oropharynx and the salivary glands and, subsequently, the lymphocytes in the tonsillar crypts. EBV-infected B cells are then responsible for disseminating the infection throughout the lymphoreticular system. By infecting the B cells, the virus is passed on to progeny cells over the years, thus evading immunoclearance.⁵ The cellular response to EBV includes EBV-specific cytotoxic T-lymphocytes, as well as atypical lymphocytes consisting of both CD8+ T cells and CD16+ natural killer cells. Despite this immune response, however, EBV becomes a latent lifelong infection.

Acute EBV infection is synonymous with heterophil-positive IM, and is classically characterized by fever, pharyngitis, lymphadenopathy, and a peripheral blood smear with at least 50% mononuclear cells and 10% atypical lymphocytes.⁶ However, up to 15% of symptomatic patients do not meet all four criteria.⁷ The most frequent symptoms of IM include sore throat, malaise, headache, abdominal pain, nausea, or vomiting. Clinical signs include lymphadenopathy, fever, pharyngitis or tonsillitis, and splenomegaly. Less common manifestations include hepatomegaly, rash, periorbital edema, palatal enanthem, and jaundice. Most cases of IM are self-limited and recover fully, although deaths from splenic rupture, upper airway obstruction, and bacterial superinfection have been reported. Other rare manifestations include

central nervous system complications, myocarditis, pleural effusion, vasculitis, and interstitial nephritis.⁸

Because most infected individuals are exposed to EBV early in life, acute infection is less frequently diagnosed in older adult and elderly patients. However, when IM afflicts the older population, the symptoms and signs are often atypical, so that IM is usually not even considered in the initial differential diagnosis. Several studies have investigated the discrepancy in the signs and symptoms of IM between younger and older patients. In an earlier paper evaluating age-related differences in the presentation of IM, Horwitz and colleagues examined clinical and laboratory data from 7 patients with heterophil-antibody positive IM from 40 to 78 years of age.⁹ None of the patients met all of the clinical criteria for IM, although serologic testing confirmed acute EBV in all 7 of them. Furthermore, prominent lymphadenopathy, an essential component of IM, was present in only 2 of 7 patients. In another study, Halevy and Ash¹⁰ compared the clinical and laboratory features of IM in the young (defined as 10–17 years of age) to patients over the age of 40. Older patients were less likely to present with lymphadenopathy (25% vs 94%, $P < .001$), splenomegaly (50% vs 76%, $P < .05$) and pharyngitis (25% vs 47%, $P < .05$).¹⁰ In addition, older patients demonstrated a longer duration of fever compared to their younger counterparts (14 days vs 7 days, $P < .01$). Although not statistically significant, older patients also tended to have more jaundice (33% vs 18%).¹⁰ Schmader and colleagues looked specifically at 29 elderly patients (defined as age > 60 years) and found relatively lower rates of lymphadenopathy, pharyngitis, and splenomegaly, but higher rates of jaundice.¹

Another confounding reason for the misdiagnosis of acute EBV in older adults is the presence of atypical laboratory findings. Axelrod and Finestone reported that bilirubin levels were greater than 2 mg/dL in 3% of younger patients (age < 35 years) compared to 30% of older patients (age > 40 years).² Although this study reported comparable levels of AST and AP in both age groups, other studies have reported substantially higher AST and GGT values in older individuals compared to teenagers.¹¹ A common IM laboratory finding is the presence of atypical lymphocytes in the peripheral blood smear. Axelrod and Finestone found that 23% of older adults had fewer than 50% lymphocytes in peripheral blood smear and 16% had less than 5% atypical lymphocytes.² In addition, older patients had a significantly lower peak total WBC count than the younger group (6,600/ μ L vs. 11,000/ μ L, $P < .001$).¹⁰ Interestingly, about 10% of patients aged 40–72 years did not mount a heterophil antibody response in the setting of IM.¹¹ Lastly, heterophil antibody-positive patients tended to be younger than heterophil-negative patients.¹²

In general, hepatic abnormalities are present in 80–95% of IM patients, and most abnormalities consist of self-limited elevations of the serum AST. Enzyme levels tend to peak in the second to third week of illness but generally resolve within 90 days of the onset of illness.^{13–15} Earlier studies described serum AST as the most frequently elevated liver function test (occurring in 96.7% of patients), with the average peak value at 213 IU/L.¹⁵ This finding has also been confirmed in other studies.^{13,16}

Similar elevations in serum ALT have been observed in recent studies.¹⁷ Increased bilirubin levels have been reported reaching up to 35% of IM patients, with levels exceeding 20 mg/dL in some cases.^{11,15} Elevations in AP are also detectable in up to 75% of cases,^{15,18} with levels as high as 1,440 U/L in some instances.^{17,19,20} Notably, marked elevations in AP have also been seen in association with normal or near-normal serum bilirubin concentration in about 65% of IM patients.¹⁸ These cholestatic changes have been postulated as resulting from EBV's inhibition of the main bilirubin transporter or from direct virus-induced self-limited cholangiocyte damage.¹⁷ Although a number of cholestatic hepatitis cases have been reported in the literature between 1966 and 2004,²¹ very few were in older adults and elderly patients.^{14,20–24} In several of these cases, the clinical presentations of jaundice and fever were mistaken for biliary obstruction, resulting in unnecessary diagnostic evaluations and a delay in diagnosis.

Neurologic involvement is encountered less commonly in IM, with a reported incidence of 0.44 cases per million patients per year.²⁵ Neurologic manifestations have included Guillain-Barre syndrome, cranial nerve palsies, optic neuritis, meningoencephalitis, aseptic meningitis, encephalomyelitis, transverse myelitis, peripheral neuritis, and multiple sclerosis.²⁶ The pathogenesis of EBV-associated neurologic disorders is not completely understood, but direct viral invasion of the central nervous system is a possible mechanism. Alternatively, neurologic injury may be immunologically mediated by infiltration of cytotoxic CD8+ lymphocytes into neural tissue or deposition of antibody-antigen complexes.²⁶ In a series of 8 patients, the most common manifestation was acute encephalitis (50%), with acute cerebellar ataxia, acute disseminated encephalomyelitis, myelitis, and meningitis, accounting for the remainder. Most of the affected patients were young adults; only 30% of the patients were older than 40, and only 1 patient was over the age of 60.²⁵ McKendall and coworkers also reported a case of a patient with acute EBV infection and secondary encephalomyelitis who, similar to our second patient, also presented with SIADH.²⁷

The individual immunologic response to primary EBV infection likely determines the nature and severity of symptoms. The tendency toward a more symptomatic

reaction to the virus is, in part, related to the more heightened immune response in older patients than in infants and children.²⁸ Indeed, Ouyang and colleagues demonstrated a clonal expansion of EBV antigen peptide-specific CD8+ T cells in the elderly, with a significant decrease in the fraction of cells capable of secreting interferon-gamma after being stimulated by a specific antigenic peptide. They concluded that the clonally expanded EBV-specific T cells in the elderly are mostly dysfunctional, occupying immunologic space and potentially leading to a shrinkage of the T cell repertoire for other novel antigens.²⁹

Our 2 patients with acute EBV presented with atypical symptoms and did not mount a significant atypical lymphocytosis. Our first patient's heterophil antibody test was negative. Both of our patients demonstrated cholestatic hepatitis and neurologic involvement with EBV. In both patients, an extensive diagnostic work-up was undertaken, including evaluations of the hepatobiliary tract and the central nervous system, as well as tests for fever of unknown origin. In both cases, the ultimate diagnosis of IM may have been delayed due to an initial lack of suspicion for acute EBV.

The diagnosis of acute EBV in older patients requires recognition of potentially atypical laboratory findings. Heterophil antibodies are the first-line diagnostic tools for IM. These antibodies appear within 1 week following the onset of illness, peak during weeks 2–5, and persist for up to 1 year. However, due to the high prevalence of heterophil-negative IM in patients with increasing age,³⁰ patients suspected of having IM who are heterophil-negative should be tested for EBV-specific antibodies, ie, EBV VCA antibody, EA antibody, and the anti-EBV nuclear antigen (EBNA). Anti-VCA IgM is most useful in diagnosing acute IM because titers are elevated only during the first 2 months of the disease. In contrast, anti-EBNA antibodies appear 6–12 weeks after onset of symptoms. Thus, a positive EBNA early in the disease course excludes a diagnosis of acute IM and instead suggests a reactivation.³ However, single elevated titers of anti-EA, IgG anti-VCA, and immunoglobulin A (IgA) anti-VCA in older adults must be interpreted with caution, because a relatively high prevalence of elevated antibodies in healthy individuals has also been reported.¹ Incidentally, EBV DNA has also been detected in the CSF of patients without neurologic symptoms.²⁶

As with our patients, many adults with acute EBV are hospitalized for the evaluation of their presenting symptoms.¹⁰ However, the treatment in most cases remains supportive. Systemic corticosteroids are utilized in cases of impending airway obstruction, profound thrombocytopenia, or hemolytic anemia.³ Steroids have also been used and described in several case reports of severe central nervous system or cardiac disease or in patients with severe

malaise and prolonged fevers. To date, no systematic evaluation has found that corticosteroids help patients regain normal liver function. Antiviral agents, such as acyclovir, have not been found to affect the severity or duration of IM, but they do appear to reduce oropharyngeal shedding of the virus.³¹ In a double-blind, placebo-controlled trial, acyclovir combined with prednisolone inhibited oropharyngeal EBV replication without affecting the duration of clinical symptoms or the development of EBV-specific cellular immunity.³²

Conclusion

In elderly patients presenting with nonspecific symptoms, including fever, liver chemistry test abnormalities, and neurologic symptoms, IM should be considered in the differential diagnosis, and appropriate diagnostic evaluation should be undertaken. Costly and invasive procedures can be duly avoided if an appropriate diagnosis is achieved earlier in the course of the illness.

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Review

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Epstein-Barr virus (EBV) is ubiquitous across the world, and most infected individuals are seropositive for EBV by the time they are young adults. The primary EBV infection is usually asymptomatic but sometimes causes infectious mononucleosis (IM). Hepatobiliary problems are very common, particularly mild hepatic involvement

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Table 1. Two-Step Diagnostic Algorithm for Hepatitis Secondary to Epstein-Barr Virus Infection

Confirmation Step	Exclusion Step
<ul style="list-style-type: none"> • Altered liver function tests <ul style="list-style-type: none"> – AST and ALT • Serological evidence of EBV activity <ul style="list-style-type: none"> – Viral capsid antigen IgM – Viral capsid antigen IgG • Histopathological changes <ul style="list-style-type: none"> – Sinusoidal lymphocytic infiltration • Viral genome identified in liver tissue by PCR 	<ul style="list-style-type: none"> • Alcohol consumption >40 mL per day • Diabetes or impaired glucose tolerance • Body mass index <18 kg/m² or >26 kg/m² • Dyslipidemia • Impaired thyroid function tests • Gluten enteropathy • Prior confirmed chronic liver disease • Autoimmune hepatitis, primary biliary cirrhosis • Viral hepatitis B or C • Hereditary hemochromatosis or iron overload • Wilson disease • Hepatotoxic drug use in the past 12 months • Hereditary muscular disorder

AST = aspartate aminotransferase; ALT = alanine aminotransferase; IgM = immunoglobulin M; IgG = immunoglobulin G; PCR = polymerase chain reaction.

(in 80%–90% of cases), which present as asymptomatic and self-limited elevation of transaminases, typically to 2–3 times above the upper limit of normal.¹

Recently, Hara and colleagues have suggested that pathogenic mechanisms can explain the hepatic involvement of EBV.² These authors studied peripheral blood mononuclear cells from 4 patients with severe EBV hepatitis and jaundice, and found that EBV mainly infected T cells, whereas EBV mainly infected B cells in patients with IM. T lymphocytes express fewer viral antigens than B cells and, therefore, exhibit greater immune evasion, which might explain the severity of some EBV cases with hepatic involvement. In the study by Hara and colleagues, the liver was biopsied in 3 patients with severe hepatitis, and spotty necrosis of the liver parenchyma with destruction of the limiting plate was found. Interestingly, *in situ* hybridization assays showed that lymphocytes, not hepatocytes, were infected, and it was confirmed that these were CD8+ T cells. Animal studies have suggested that activated CD8+ T cells are selectively trapped in normal livers, primarily through intracellular adhesion molecule 1 (ICAM-1), which is expressed in the sinusoidal endothelium and Kupffer cells.^{3,4} These findings suggest that EBV-infected cells and activated CD8+ T cells may undergo uncontrolled clonal expansion, accumulating in the liver and causing hepatocellular injury through interferon-gamma, tumor necrosis factor alpha, and Fas ligand.⁵

LoSavio and Te describe 2 clinical cases in older adults, in whom mild cholestatic hepatitis led to a diagnosis of acute EBV infection despite atypical presentations.⁶ This is an interesting problem in this growing

age group.⁷ In the first case, a 73-year-old woman with many medical problems presented with confusion, fever, and abnormal gamma-glutamyl transferase activity, and later developed hyperbilirubinemia and elevated alkaline phosphatase levels. After extensive testing and despite the absence of heterophilic antibodies (a common finding in this age group), the presence of EBV viral capsid immunoglobulin M antibodies led to the diagnosis of EBV. The patient's disease progression was good and required no specific therapy. In the second case, a 59-year-old woman presented with malaise, occasional fevers, bradylalia, hyponatremia, and abnormal liver enzyme activities, and subsequently developed hyperbilirubinemia and lower extremity pain with abnormal reflexes. A diagnosis of acute EBV infection complicated with encephalomyelitis and cholestatic hepatitis was established. Again, in terms of liver involvement, her disease progression was good and required no specific therapy.

In these cases, the diagnosis of cholestatic hepatitis due to EBV was established based on clinical suspicion and associated findings related to multiorgan involvement. Cholestatic hepatitis due to acute EBV infection in the elderly is rare, and it is usually difficult to diagnose because similar responses in liver function tests are common in other infectious and noninfectious processes.⁸ We recommend a two-step diagnostic algorithm when EBV hepatitis is suspected, as shown in Table 1 (based on data from Petrova and associates⁹ and Drebber and associates¹⁰).

Medical therapy for EBV cholestatic hepatitis is restricted to supportive measures in most cases.¹¹ How-

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ever, the severity and duration of some cases has led to different interventions, from antiviral agents to Molecular Adsorbents Recirculation System (MARS) therapy¹² and orthotopic liver transplantation.¹³

Finally, we believe that hepatic involvement in EBV infection is a field that requires systematic clinical research to define diagnostic and therapeutic guidelines. In the meantime, highly comprehensive clinical accuracy and judicious use of therapeutic options is the most useful and secure approach.

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