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Hepatitis viruses: Not always what it seems to be

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ABSTRACT

The classic hepatotropic viruses, hepatitis A through E, are not the only viral agents able to infect the liver. Other systemic viruses may cause hepatic injury that can range from mild and transient elevation of aminotransferases to acute hepatitis and occasionally acute liver failure and fulminant hepatitis. The clinical presentation may be indistinguishable from that associated with classic hepatotropic viruses. These agents include cytomegalovirus; Epstein-Barr virus; herpes simplex virus; varicella-zoster virus; human herpesvirus 6, 7, and 8; human parvovirus B19; adenoviruses among others. Wide spectrums of clinical syndromes are associated with cytomegalovirus disease. Unique clinical syndromes may present in neonates, young adults and immunocompromised hosts infected with cytomegalovirus. Cases of fulminant hepatitis have been reported in both immunocompromised and immunocompetent hosts infected with Epstein Barr virus. Occasionally, these patients with acute hepatic failure may need liver transplantation. Herpes simplex viruses may involve the liver in neonatal infections, pregnancy, immunocompromised hosts and occasionally, immunocompetent adults. Varicella-Zoster virus has also been associated with severe acute hepatitis and fulminant hepatitis in adults. The drug of choice for these conditions is intravenous acyclovir. These may also need liver transplantation in the more severe forms of clinical presentation. Typical liver biopsy findings can be useful in determining the diagnosis of these viral infections. Human herpesviruses 6, 7, and 8, human parvovirus B19, and adenoviruses can also be present with features of acute liver injury and occasionally as fulminant hepatitis. The clinical syndromes are less well delineated than those associated with herpesviruses. It is important to consider these viruses as possible etiologic agents in patients who have acute liver injury and their serologic markers for the classic hepatotropic viruses are not indicative of an active infection.

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Los virus de las hepatitis no siempre son los habituales

Los agentes de la hepatitis viral A, B, C, D y E no son los únicos virus que pueden causar un síndrome de daño hepático agudo. Agentes virales como el citomegalovirus, Epstein-Barr, herpes simplex 1 y 2, varicella-zoster, virus herpes humano 6, 7, y 8, parvovirus B19 y adenovirus pueden causar daño hepático agudo e inclusive presentarse como hepatitis fulminante. Los cuadros clínicos de daño hepático agudo por citomegalovirus, Epstein Barr y herpes simplex 1 y 2 han sido caracterizado mejor. Se

ha intentado el uso de drogas antivirales específicas como el uso intravenoso de aciclovir. Ocasionalmente, se ha requerido el trasplante hepático para rescatar pacientes con hepatitis fulminantes por estos agentes virales. La biopsia hepática puede ser de utilidad en estos casos puesto que los hallazgos son bastante característicos. La expresión clínica asociada a infecciones por virus herpes humano 6, 7 y 8, parvovirus B19 y adenovirus son menos características. Ha habido varios casos de hepatitis fulminante causada por estos agentes virales. Estos agentes virales deben ser considerados en el diagnóstico de casos de daño hepático agudo e inclusive hepatitis fulminante cuando los marcadores virales para los virus de hepatitis A-E son negativos.

The classic hepatotropic viruses, hepatitis A through E, are not the only viral agents capable of infecting the liver. Other viruses may affect the liver as part of organ-specific or systemic involvement, with hepatic injury that can range from mild and transient elevations in aminotransferases to acute hepatitis and occasionally acute liver failure and fulminant hepatitis (FHF). Their ability to cause chronic liver disease has not been proven unequivocally. These agents include cytomegalovirus; Epstein-Barr virus; herpes simplex virus; varicella-zoster virus; human herpesvirus 6, 7, and 8; human parvovirus B19; adenoviruses; among others.

Cytomegalovirus

Human cytomegalovirus (CMV)[1] is the largest member of the betaherpesviridae family. The cellular response to CMV infection is characterized by cytomegaly and prominent intranuclear inclusion bodies (Figure 1). CMV infections are common, affecting 60%-70% of adults, and play a significant role as an opportunistic pathogen in immunocompromised hosts. Early recognition of infection, institution of therapy, and prevention of infection are critical in altering the outcome in these patients[2].

Several factors determine the manifestations and severity of CMV infection. Infection is acquired either in the perinatal period and infancy or in adulthood through sexual contact, blood transfusions, or organ transplantation. Most primary CMV infections in immunocompetent adults are asymptomatic or associated with a mild mononucleosis-like syndrome. As with other herpes viruses, all primary infections resolve and enter into lifelong latency in which live virus is sequestered in a nonreplicative state. Persons with latent infection and intact immune system have no symptoms but exhibit antibodies to CMV. Circulating lymphocytes, monocytes, and polymorphonuclear leukocytes may serve as the predominant site of viral latency. The risk for intermittent reactivation is increased with immunosuppression. In immunocompromised patients, CMV disease can result from either a primary infection, or more commonly, from reactivation of latent infection. Although adequate anti-CMV antibodies are detected during episodes of infection reactivation, cell-mediated immunity, characterized by decreased numbers of cytotoxic T lymphocytes and natural killer cells, is defective. The incidence and severity of CMV disease closely parallels the degree of cellular immune dysfunction[3].

A wide spectrum of clinical syndromes are associated with CMV disease ranging from asymptomatic infection to life-threatening congenital CMV syndrome in neonates, infectious mononucleosis syndrome in young adults, to severe pulmonary, retinal, neurological, gastrointestinal, and hepatic diseases in immunocompromised hosts, in whom CMV is a very common opportunistic pathogen.

In immunocompetent children and adults, CMV infection is usually subclinical but sometimes can cause a disease that resembles Epstein-Barr virus (EBV) infectious mononucleosis syndrome[4].

Liver dysfunction is commonly associated with CMV mononucleosis. It is usually mild and rarely symptomatic in the immunocompetent patient. Hepatosplenomegaly and laboratory evidence of mild to moderate hepatic dysfunction are the predominant features, with increased aminotransferases and alkaline phosphatase in 88% and 64% of cases, respectively, but lower than commonly

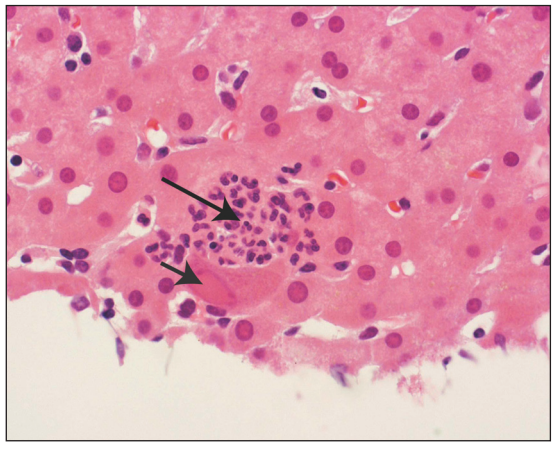

Figure 1. CMV hepatitis. the long arrow shows a microabscess and the short arrow a CMV nuclear inclusion. Magnification 100x; hematoxylin and eosin stain.

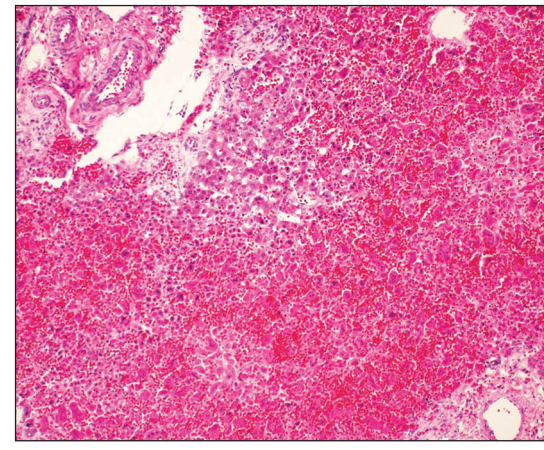

Figure 2. Massive hepatic necrosis due to HSV-1. Magnification 20x; hematoxylin and eosin stain.

encountered in active viral hepatitis[5]. Rare manifestations of CMV hepatitis include tender hepatomegaly, granulomatous hepatitis, anicteric or icteric cholestatic hepatitis, and acute hepatitis with massive necrosis.

In patients with impaired cell-mediated immunity, disseminated CMV infection results in serious life threatening diseases. CMV is the most common opportunistic viral infection in AIDS patients causing retinitis, central nervous system infections, esophagitis, and colitis. CMV may also invade the hepatobiliary tract in AIDS patients causing hepatitis, pancreatitis, and acute acalculous cholecystitis[6,7]. The presence of cytomegalovirus retinitis, gastrointestinal disease, or viremia in AIDS patients increases the risk for the development of a cholestatic syndrome caused by papillary stenosis and sclerosing cholangitis (AIDS cholangiopathy), which does not usually respond to antiviral therapy[8]. Other immunocompromised patients at risk are organ transplant recipients.

The diagnosis of CMV hepatitis requires confirmatory laboratory tests. Serologic studies of CMV-IgM antibodies may be helpful in primary infections in immunocompetent hosts. Viral culture techniques could be greatly enhanced with the use of "shell vial" assays, using CMV early antigens[9]. Using molecular techniques to detect CMV early antigen or the CMV DNA, increases the sensitivity of detecting CMV infection in blood or tissue[10].

To clearly establish the diagnosis of active CMV infection, it is necessary to have histological evidence of cellular injury associated with infection. Distinct pathologic findings on liver biopsy are important in establishing the diagnosis of CMV hepatitis, especially in the immunocompromised host. Giant multinucleated cell reaction with an inflammatory response, multifocal necrosis, and biliary stasis are commonly found. Large nuclear inclusion-bearing cells, so-called "owl's eye" inclusions, can be found in hepatocytes or bile duct epithelium[11].

Hepatitis is the most frequent organ-specific complication from CMV infection after liver transplantation, affecting approximately 10% of recipients; with a higher incidence among seronegative recipients compared to seropositive patients, 26% vs 9%. In these cases, infection generally occurs as a consequence of reactivation rather than primary infection.

Treatment of CMV with antiviral agents is not always indicated, especially in self-limited disease in immunocompetent adults. For severe cases, particularly in patients with impaired cell-mediated immunity, therapy can be life saving. Drugs approved for treatment of CMV disease include ganciclovir, valganciclovir, foscarnet and cidofovir. Ganciclovir is considered the antiviral agent of choice against CMV. The duration of therapy should be guided by repeated measurements of CMV in blood samples. Emerging strains resistant

to ganciclovir pose a therapeutic challenge, where foscarnet or cidofovir may become alternative antiviral agents[12]. A more recent addition is valganciclovir, which has been evaluated among liver transplant recipients with CMV disease[13].

Epstein-Barr Virus

Epstein-Barr Virus (EBV) shares the characteristic morphologic features of the Herpesviridae family. Its genome consists of a linear DNA molecule that encodes nearly 100 viral proteins. After infecting B-lymphocytes, the linear EBV genome becomes circular, forming an episome, which usually remains latent in these B cells. Viral replication is spontaneously activated in only a small percentage of latently infected B cells[14]. EBV infection is a very common and life-long infection affecting over 90% of humans worldwide.

Transmission of EBV usually occurs by contact with oral secretions. Although rare, transmission through blood transfusion has been reported. EBV replicates in nasopharyngeal epithelial cells, and seropositive persons actively shed virus in saliva. B cells in the oropharynx may be the primary site of infection. Resting memory B cells are thought to be the site of persistence of EBV within the body. Various clinical conditions have been associated with EBV, such as infectious mononucleosis, Burkitt's lymphoma, nasopharyngeal carcinoma, Hodgkin's disease, peripheral T-cell lymphoma, and post-transplant lymphoproliferative disease[15].

Liver involvement is well recognized in EBV infection. Manifestations of liver involvement range from the mild self-limiting acute hepatitis to occasional reports of fatal acute fulminant hepatitis[16].

Mild elevation of aminotransferases and elevated lactic dehydrogenase are seen in up to 90% of cases of infectious mononucleosis. Typically, the rise in aminotransferases is gradual, reaching a peak that is lower than that commonly encountered in acute viral hepatitis. Patients older than 30 years generally have a more severe disease than children. Mild elevation of alkaline phosphatase is also seen in 60% and mild hyperbilirubinemia in about 45%.

Severe cholestatic jaundice and right upper quadrant abdominal pain may occur in elderly patients. Jaundice may occasionally be the initial clinical presentation, in combination with fever and abdominal pain, and can be mistaken for extrahepatic biliary obstruction. Jaundice predominantly occurs when EBV infection is complicated with autoimmune hemolytic anemia, and occasionally as a direct result of virus-induced cholestasis[17,18].

Other occasional clinical settings for EBV liver involvement include post-transfusion hepatitis, granulomatous hepatitis, and fatal fulminant hepatitis. In some cases of granulomatous hepatitis, serologic evidence of chronic EBV infection was found[19,20]. Cases of fatal fulminant hepatitis with massive hepatic necrosis and disseminated intravascular coagulation have been reported in both immunocompromised and immunocompetent hosts[21-23].

Diagnosis of infectious mononucleosis is established on the basis of clinical features, laboratory and serological findings indicative of a recent EBV infection. The most common hematological findings include leukocytosis in 70% of cases, with predominantly lymphocytosis and monocytosis, and mild thrombocytopenia in up to 50%. The "monospot" test that detects heterophil antibodies, while sensitive, is not very specific. EBV-specific IgG and IgM antibodies, directed against the viral capsid antigens-VCA, early antigens -EBV anti-D and anti-R, nuclear antigen-EBVNA, and soluble complement-fixing antigens -anti-S, improve sensitivity and specificity in detecting the infection[24]. In the vast majority of cases there is no indication for liver biopsy, but when performed there may be portal and sinusoidal mononuclear cell infiltration with focal hepatic necrosis or fatty infiltration. Of particular utility as diagnostic methods are *in situ* hybridization, Southern blot analysis, and polymerase chain reaction to identify specific RNA or DNA sequences in the involved organs[25].

There are no specific diagnostic criteria for EBV hepatitis, but it is generally agreed that the following need to be present to establish the diagnosis: elevated aminotransferases, active EBV infection as defined by serology, typical pathologic changes on biopsy and demonstration of the viral genome in liver tissue by molecular methods.

There is no specific drug or treatment for EBV infection. Acyclovir inhibits EBV *in vitro* replication and reduces viral shedding in the oropharynx but has no effect on the symptoms of infectious

mononucleosis which are primarily due to the immune response against the virus and therefore not recommended[26]. Ganciclovir has been shown to be effective in the treatment of EBV hepatitis in a small number of children[27]. There is a single report of fulminant hepatic failure in an immunocompetent young girl caused by EBV infection that was treated by liver transplantation[28].

Herpes Simplex Virus

Herpes simplex viruses, HSV-1 and HSV-2, commonly infect humans and produce a wide variety of illnesses. The clinical manifestations and course of HSV infections depend mainly on the site involved and the patient's age and immune status.

Occasionally, HSV viremia results in visceral involvement, affecting mainly three organs: esophagus, lungs, and liver. Liver involvement occurs in the following settings: neonatal infections, pregnancy, immunocompromised hosts, and rarely, immunocompetent adults.

In neonates, hepatitis occurs with multi-organ involvement and usually carries a high mortality rate[29,30]. Delay in antiviral therapy, while awaiting confirmation of diagnosis, can lead to very poor outcomes[31].

HSV hepatitis in pregnant women was first reported in 1969 and was seen in the context of disseminated primary infection, generally during the third trimester and presenting as fulminant hepatitis[32,33]. Mucocutaneous lesions are present in only half of cases; therefore, the clinical suspicion for diagnosis of this condition must be high. Twenty-five percent of cases were not diagnosed until autopsy. Early recognition with initiation of antiviral therapy may reverse an otherwise fatal process[34,35].

HSV is an uncommon cause of hepatitis in immunocompetent patients. A mild asymptomatic elevation of aminotransferases levels can be detected in 14% of healthy adults with acute genital infection[36]. Fulminant hepatitis with more than 100-fold rise in aminotransferases was reported and associated with a favorable outcome after antiviral therapy[37]. In immunocompromised hosts, HSV hepatitis has occurred during primary and, rarely, during recurrent infection, with a triad of fever, leukopenia and markedly elevated liver enzymes.

Liver biopsy is essential to establish the diagnosis of HSV hepatitis, especially in pregnancy. It usually shows focal, sometimes extensive, hemorrhagic or coagulative necrosis of the hepatocytes with limited inflammatory response (Figure 2). Typical intranuclear inclusions (Cowdry type A) are often identified at the margins of the foci of necrosis. The diagnosis is confirmed by detection of HSV DNA sequences by molecular techniques, which are more sensitive than tissue culture methods[34,38,39].

HSV hepatitis is an infectious disease emergency associated with a rapid and lethal course, and requires early recognition and institution of antiviral therapy, while awaiting confirmation of diagnosis, in order to improve outcome[40,41]. At Mayo Clinic, the incidence of HSV hepatitis was reported to be 6% among all fulminant hepatitis cases from 1974 to 1982[42]. High dose acyclovir (at least 10 mg/kg/day every 8 hours) is the antiviral drug of choice[34, 43-45]. Newer drugs with improved oral bioavailability include valacyclovir and famciclovir, but they are not generally indicated in severe forms of HSV infection. Shanley[46] reported a case of a healthy female who developed disseminated HSV-2 infection and fulminant hepatitis during the third trimester of pregnancy requiring high dose antiviral therapy, which resulted in eradication of HSV mucocutaneous lesions. However, the patient's condition continued to deteriorate leading to liver transplantation. Recurrence was not observed, suggesting that disseminated HSV infection should not be an absolute contraindication for transplantation in certain clinical settings. Several series have also demonstrated the utility of liver transplantation in this setting[47,48].

Varicella-Zoster virus

Varicella-Zoster virus (VZV) causes two distinct clinical diseases. Varicella is the primary infection, which is characterized by a benign generalized exanthematous rash. Recurrence of infection results in a localized phenomenon known as herpes zoster. Rare, non-cutaneous manifestations, such as encephalitis, pneumonitis, myocarditis, and hepatitis, may accompany the skin rash, especially in immunocompromised patients[49].

Mild and transient liver enzyme abnormalities can occur in up to 25% of children with varicella[50].

Primary infection in immunocompetent adults may cause severe acute hepatitis with more than tenfold increase in aminotransferases[51] and, sometimes, fulminant hepatic failure with evidence of VZV in liver and other organs[52].

In contrast to the rather benign course of zoster (reactivation of infection) in the setting of organ transplantation, primary varicella infection can be quite aggressive[53]. Visceral involvement, including the liver, may occur in the immediate postoperative period or up to several months after transplantation. It is usually associated with rapid onset and fatal fulminant hepatitis[54-56].

Serologic testing is of little value, especially in immunocompromised patients. Confirmation of diagnosis is possible through the isolation of VZV from skin lesions or from the affected organs. Liver biopsy often shows foci of coagulative necrosis and intranuclear inclusions with an inflammatory response. PCR and immunoperoxidase techniques are helpful to distinguish VZV from HSV hepatitis.

Centers for Disease Control (CDC, Atlanta, GA, USA) guidelines for the prevention and control of nosocomial infections are useful for infection control in hospital personnel[57]. Early administration of antiviral therapy is critical in the setting of VZV hepatitis, especially in immunocompromised patients. The drug of choice is intravenous acyclovir at a dose of 10 mg/kg every 8 hours for 7 to 10 days[58,59].

Human Herpesvirus 6

Nearly all infants by the age of 2 are infected by human herpesvirus 6 (HHV-6) which usually results in exanthema subitum also known as Roseola Infantum or Sixth Disease[60]. Attempts to prove an etiologic association of HHV-6 with liver injury have been inconclusive[61]. PCR techniques and in situ-hybridization led to isolation of HHV-6 from the liver tissue of infants with chronic hepatitis, suggesting HHV-6 as a causative agent[62,63]. Reactivation of infection may occur after solid organ transplantation with questionable clinical significance[64].

A recent study reported[65] the involvement of HHV-6 in 15 patients with non-A and non-E hepatitis who underwent liver transplantation for acute liver failure. HHV-6–specific antigens were analyzed in the explanted livers by immunohistochemistry, and the possible presence of the virus in peripheral blood mononuclear cells was demonstrated by HHV-6 antigenemia test. Of the 15 patients with acute liver failure of unknown cause, 12 demonstrated HHV-6 antigens in the liver. Most of these patients also demonstrated HHV-6 antigenemia. No other viruses were identified in liver tissue from these patients, leading the authors to speculate that HHV-6 may be a cause of acute liver failure. Although other investigators have detected HHV-6 in patients with acute hepatitis and fatal FHF[65,66], these reports do not necessarily establish causality. This virus may be associated with hepatitis in liver transplant recipients; and the therapy of choice is ganciclovir or foscarnet[67]. Foscarnet has a better in vitro virus sensitivity than acyclovir and ganciclovir against HHV-6[68].

Human Herpesvirus 7 and 8 (HHV-7 and HHV-8)

HHV-7 also infects all humans by the age of 5 years causing febrile syndromes. Hepatitis in association with HHV-7 has been infrequently reported[69].

HHV-8, also called Kaposi's sarcoma-associated human herpesvirus 8, has been detected consistently in Kaposi's sarcoma, lymphoma, multicentric Castleman's disease, in HIV- positive patients and occasionally in HIV- negative patients. Liver involvement may occur in Kaposi's sarcoma and other HHV-8 related malignancies in immunosuppressed patients, particularly in the setting of primary acute disseminated infection, such as seen in transplant recipients from an infected donor allograft or, less commonly, during HHV-8 reactivation in HIV-infected individuals.

Human Parvovirus B19

Human parvovirus B19 (HPV B19) is a small DNA virus from the parvoviridae family[70].

Human parvovirus B19 infection produces a spectrum of clinical manifestations including: erythema infectiosum or "fifth disease," in children; hydrops fetalis and fetal death; an arthritis syndrome associated with acute infections in adults; hematological disorders such as leukopenia, thrombocytopenia, transient aplastic crisis in patients with chronic hemolytic anemia, and

chronic anemia in immunocompromised patients; other rare organ involvement include neurologic, cardiac, hepatic disease, and vasculitis.

Hepatic manifestations range from a transient elevation of serum aminotransferases[71,72] sometimes seen during the course of erythema infectiosum[73,74] to FHF[75]. HPV-B19 DNA has been found in liver samples from 67% of patients with non-A and non-E FHF and aplastic anemia, in 50% of patients with cryptogenic FHF without aplastic anemia, compared to 15% of control subjects with chronic liver failure. This led some investigators to suggest that HPV-B19 is a possible causative agent of FHF[76,77].

In most cases, HPV-B19 infection is a benign and self-limited infection and requires no treatment other than symptomatic relief[78]. At Mayo Clinic, we reported two cases of a less severe form of hepatitis-associated aplastic anemia[79].

Adenoviruses

There are close to 50 serotypes of adenoviruses causing acute infections of the respiratory system, conjunctivae, and gastrointestinal tract, and occasionally hemorrhagic cystitis, infantile diarrhea, intussusception, and central nervous system infections. Disseminated disease with multi-organ involvement has been reported in immunocompromised, and occasionally immunocompetent, patients and associated with an increased mortality[80,81].

The role of adenovirus as an etiologic agent of hepatic damage has been controversial. Fatal cases of adenovirus infection with FHF were reported in immunosuppressed adults. Postmortem liver pathology revealed widespread hepatic necrosis with intranuclear inclusions within viable hepatocytes. Electron microscopy may show crystalline arrays of virions within hepatocytes[82]. Although no specific therapy for adenovirus hepatitis is currently available; cidofovir has been recently suggested to play a role in the treatment of adenovirus infection[83].

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