Herpes Virus Infections

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There are nine distinct herpes viruses capable of causing infection in humans. Many clinical syndromes are associated with human herpes viruses, including cutaneous lesions, mononucleosis, retinitis, pneumonitis, and hepatitis. Hepatitis has been described in herpes simplex virus-1 (HSV-1) and HSV-2, varicella zoster virus, cytomegalovirus (CMV), Epstein-Barr virus (EBV), and human herpes virus-6. This article will focus on CMV and EBV, which are associated with the highest rate of hepatic involvement.

Epstein-Barr Virus

EBV is found worldwide, and nearly 95% of humans have EBV antibodies by adulthood. Although most widely known for causing infectious mononucleosis, EBV is also associated with Burkitt's lymphoma, Hodgkin's lymphoma, and nasopharyngeal carcinoma, along with central nervous system (CNS) lymphomas in AIDS and posttransplant lymphoproliferative disorders (PTLD) in transplant recipients.¹

Pathogenesis

Primary EBV infection is spread by exposure to oral secretions from seropositive persons. Most cases occur through asymptomatic shedding of the virus. After primary infection, EBV remains latent in B cells.

The exact mechanism of EBV-induced hepatitis remains unknown. On histology, acute infectious mononucleosis causes mild portal inflammation, with lymphocyte infiltration of the portal tract and sinusoids. The bile ducts and hepatic arterioles are usually spared. In severe EBV hepatitis, spotty necrosis of the liver parenchyma has been demonstrated. Additionally, in situ hybridization studies have found that EBV remains in CD8⁺ T lymphocytes that infiltrate the liver; it does not directly invade hepatocytes.²

Transplant recipients are at risk for primary EBV infection via latently infected donor B cells that travel with the graft. Reactivation of latent EBV can occur in the setting of immu-

nosuppressive medications and the lack of an appropriate T cell response. Treatment of graft rejection increases the risk of EBV reactivation. Both primary infection and reactivation can lead to uncontrolled proliferation of EBV-infected B lymphocytes, a condition known as PTLD.³ Half of all PTLD cases are associated with EBV, and most EBV-related cases occur within the first year of transplantation.

Clinical Manifestations

Infectious mononucleosis typically presents with fever, sore throat, and lymphadenopathy. Table 1 lists the common signs, symptoms, and hepatic laboratory abnormalities of EBV.^{1,4}

PTLD is generally suspected when a transplant recipient has a persistent, unexplained fever, particularly within the first year of transplantation. Common clinical signs and symptoms are summarized in Table 2. Focal lesions can develop in any organ, including the allograft itself.³

Diagnosis

The diagnosis of infectious mononucleosis is based on both clinical manifestations and laboratory testing. Heterophile antibodies are present in up to 90% of cases, and when positive, it is sufficient to make the diagnosis of EBV. False negative tests can occur in up to 25% of patients within the first week of illness, however. For a patient with clinical signs of infectious mononucleosis and a negative heterophile antibody, the heterophile antibody test can be repeated a week later. If an exact diagnosis is sought and the heterophile antibody is negative, testing for EBV-specific antibodies, such as anti-viral capsid antigen (VCA) and anti-EBV nucleic acid antigen (EBNA), can be performed (Fig. 1). A positive VCA IgM antibody paired with a negative anti-EBNA is highly specific for acute infection.

When PTLD is suspected, radiographic imaging with computed tomography is typically performed to look for

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; PTLD, posttransplant lymphoproliferative disorders; SOT, solid organ transplant.

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mass lesions. Brain MRI should be considered for focal neurologic findings or altered mentation. To definitively diagnose PTLD, a biopsy is required. EBV viral loads lack sensitivity and specificity for PTLD; however, higher viral loads have been associated with a higher likelihood of developing PTLD.

Treatment

Infectious mononucleosis is generally treated with supportive care. Antiviral agents do not reduce symptoms or

TABLE 1 Symptoms, Signs, and Laboratory Abnormalities in Infectious Mononucleosis*

Symptoms	Percentage	Notes
Sore Throat	82	Lasts 7-10 days; peaks at 3-5 days
Malaise	57	
Headache	51	
Anorexia	21	
Nausea	12	
Abdominal Discomfort	9	
Signs	Percentage	Notes
Lymphadenopathy	94	Anterior and posterior cervical chains
Pharyngitis	84	
Fever	76	Lasts 10-14 days; highest in first week
Splenomegaly	52	
Hepatomegaly	12	
Jaundice	5	
Lab Abnormalities	Percentage	Notes
AST and ALT	Up to 90	2-3× ULN; Rise 2 days after symptom onset, peak at 8-13 days, and return to normal around 20 days
ALP	72	<2× ULN in most cases; rise within the first few days of illness, can persist even 30 days after onset
Bilirubin	20	Typically a mild conjugated hyperbilirubinemia that normalizes within 3 weeks

AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; ALP: Alkaline Phosphatase; ULN: Upper limit of normal

*Adapted from Johannsen EC and Kaye KM¹ and Kofteridis EP et al⁴

decrease the duration of disease. No specific treatment exists for EBV hepatitis, though patients have undergone successful liver transplantation for EBV-associated acute liver failure.⁵ Treatment of PTLD generally involves a reduction in transplant immunosuppression. In localized disease, surgical resection and/or radiotherapy can be considered. Rituximab has been used as both adjuvant treatment and prophylaxis of PTLD.

Cytomegalovirus

CMV affects 30% to 97% of individuals worldwide, depending on region, with the highest rates in developing countries. The presentation of CMV varies depending on the status of a patient's immune system. Young, healthy adults with primary CMV infection often present with an infectious mononucleosis syndrome. Profound immunodeficiency caused by human immunodeficiency virus can lead to CNS disease, including retinitis and polyradiculopathy, as well as esophagitis and colitis. Recipients of hematopoietic stem cell transplant (HSCT) and solid organ transplant (SOT) are susceptible to primary infections but can also

TABLE 2 Signs and Symptoms of PTLD*

Symptoms

Unexplained fever or night sweats
Malaise
Weight loss and/or anorexia
Sore throat
Swollen glands
Headache or other focal neurologic symptoms
Liver Transplant: jaundice, abdominal pain

Signs

Pallor
Lymphadenopathy
Subcutaneous nodules
Tonsillar enlargement or inflammation
Hepatosplenomegaly
Focal neurologic signs
Incidental mass lesions found on imaging

PTLD: Posttransplant lymphoproliferative disorder

*Adapted from Green M and Michaels MG³

Figure 1 Antibodies to Epstein-Barr Virus

Figure 2 Hematoxylin and eosin staining of colonic tissue from a liver transplant recipient. The orange arrow indicates a giant cell with the characteristic cytoplasmic inclusions (upper left of the cell) and basophilic nuclear inclusions (owl's eye). Image courtesy of Temple University Hospital, Department of Pathology and Laboratory Medicine.

acquire CMV from the donated organ. In addition, reactivation of previously latent CMV occurs in the setting of immunosuppressive medications.⁶

Pathogenesis

CMV is shed from bodily fluids and commonly enters the body via the alimentary, respiratory, or genitourinary tract. SOT, HSCT, and blood transfusion are also known to transmit CMV.^{6,7} The exact mechanism of CMV transmission to target organs is unknown. Intranuclear CMV inclusions (deemed “owl’s eyes” for their appearance on histopathology; Fig. 2) can be found in virtually every organ. In cases of CMV hepatitis, cytomegalic cells are most often found in the bile duct epithelium. Less frequently, they are seen in the capillary epithelium or the liver parenchyma. In liver transplant patients, CMV has been associated with a distinct bile duct sclerosis syndrome.⁸

Clinical Manifestations

In immunocompetent hosts, CMV infection emulates the clinical presentation of EBV mononucleosis, as shown in Table 3. Liver function abnormalities occur in up to 90% of cases, but these findings are usually mild and resolve within a few weeks of infection. Nonetheless, cases of severe cholestasis, granulomatous hepatitis, and acute liver failure have been reported.⁹

Transplant recipients present in a variety of ways, depending on the type of organ or graft received. CMV has a predilection to invade the allograft¹⁰; for example, liver transplant patients are at high risk for CMV hepatitis. CMV infection can present as an asymptomatic viremia, as a viral syndrome with fever, malaise, leukopenia, and thrombocy-

TABLE 3 Comparison of Clinical Characteristics of EBV and CMV Mononucleosis

Clinical Feature	EBV	CMV
Fever	Present	Present
Lymphadenopathy	Present	Present
Lymphocytosis	Present	Present
Atypical Lymphocytes	Present	Present
Sore Throat	Often Present	Absent
Tonsillar Exudates	Often Present	Absent
Heterophile Antibody	Present (90%)	Absent

EBV: Epstein-Barr Virus; CMV: Cytomegalovirus

topenia (typically in primary infection, also called the “CMV syndrome”), or as tissue-invasive disease. Typically, CMV infection develops one to four months after transplant or the discontinuation of CMV prophylaxis. Approximately 10% of patients undergoing liver transplant will develop CMV hepatitis, and the risk is higher when the donor is CMV-seropositive. CMV hepatitis presents with prolonged fever, hyperbilirubinemia, and elevated hepatic enzymes.⁶

Diagnosis

Most cases of CMV infection in immunocompetent persons are asymptomatic, so these cases are not detected with laboratory testing. Transplant recipients and their donors are routinely tested for CMV IgG antibodies to help determine the risk for CMV reactivation. CMV polymerase chain reaction assays have become a mainstay of virus detection, particularly in transplant recipients.

Although CMV viremia in an immunocompromised patient with laboratory or radiographic evidence of tissue involvement can be suggestive of CMV disease, the definitive diagnostic test is a biopsy.⁶ For instance, it is nearly impossible to distinguish between CMV hepatitis and graft rejection without histopathology, but it is important to make the distinction because the treatment differs in terms of both antiviral agents and immunosuppression. In immunocompetent individuals, severe organ dysfunction is uncommon, so biopsy in this patient population is rarely necessary.

Treatment

CMV mononucleosis affecting immunocompetent patients is self-limiting, and treatment with antivirals is rarely needed. In SOT recipients, CMV disease is usually treated with valganciclovir. Intravenous ganciclovir is favored for severe, life-threatening illness. Foscarnet and cidofovir are used mainly in the setting of ganciclovir intolerance or resistance. Transplant recipients may require a reduction in immunosuppression in conjunction with antivirals for severe infections.¹⁰ ■

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