Infections with Herpesviruses II: Epstein-Barr Virus, Cytomegalovirus, Human Herpesviruses 6 and 7, and Kaposi’s Sarcoma–Associated Herpesvirus

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Cover Illustration by Christine Schaar
INTRODUCTION

This manual, the second installment of a 2-part series on infections with human herpesviruses (HHVs), will focus on Epstein-Barr virus (EBV; HHV-4), cytomegalovirus (CMV; HHV-5), HHV-6, HHV-7, and Kaposi’s sarcoma–associated herpesvirus (HHV-8). The first installment, published in Volume 7 Part 4 of the Hospital Physician Infectious Diseases Board Review Manual, discussed herpes simplex virus types 1 (HHV-1) and 2 (HHV-2) and varicella-zoster virus (HHV-3).

CASE PRESENTATIONS

CASE PRESENTATION 1

A 19-year-old male college student comes to the student health clinic because of a 1-week history of low-grade fever, swollen glands, mild fatigue, and an intermittent rash that only appears after soccer practice. Physical examination reveals a temperature of 37.8°C (100.1°F), mild conjunctival and oropharyngeal erythema with a few petechiae over the soft palate, moderate posterior cervical lymphadenopathy, and a spleen tip that can be palpated 2 cm below the left costal margin. No rash is present at the time of examination. Results of laboratory testing show a leukocyte count of 13.2 × 10^3/mm^3, a platelet count of 114 × 10^3/mm^3, and mildly elevated serum levels of aspartate aminotransferase (AST, SGOT) and alanine aminotransferase (ALT, SGPT).

CASE PRESENTATION 2

A 41-year-old man with AIDS calls the clinic where his condition has been followed monthly for the past 2 years to report difficulty with vision in his right eye. He says that over the past 3 to 4 days, he has intermittently seen floaters in that eye. Medical history is significant for progressive HIV disease manifested by virologic failure and a decrease in his absolute CD4+ T-lymphocyte count to 43/mm^3, despite treatment with multiple antiretroviral regimens.

CASE PRESENTATION 3

A 6-month-old female infant is brought to the emergency department by her mother shortly after having a generalized seizure. She has a 2-day history of fever, irritability, and nasal congestion. Temperature is 39.5°C (103.1°F); she is lethargic but arousable. There is no meningismus or focal neurologic findings. Analysis of cerebrospinal fluid is unremarkable. For the past 2 days, she has not attended her daycare facility, where a toddler was recently diagnosed with exanthema subitum (also referred to as roseola and sixth disease).

CASE PRESENTATION 4

A 46-year-old man who has advanced AIDS reports a 1-month history of fever, weight loss, and shortness of breath. Physical examination reveals prominent right anterior cervical lymphadenopathy, dullness to percussion at the lung bases, and hepatosplenomegaly. Results of laboratory testing show pancytopenia. Computed tomography scans of the chest and abdomen reveal bilateral hilar and retroperitoneal lymphadenopathy with small bilateral pleural effusions and hypodense lesions in the liver and spleen. Results of lymph node biopsy and cytologic analysis of pleural fluid demonstrate lymphomatous cells of similar morphology and immunophenotype.

EPSTEIN-BARR VIRUS

HISTORICAL PERSPECTIVE

EBV was known as glandular fever in the 19th century. In 1932, sheep erythrocyte agglutinins were identified...
in the sera of patients with infectious mononucleosis. Then in 1964, Epstein and associates described the presence of particles resembling herpesviruses in biopsy specimens from patients with Burkitt’s lymphoma, thus leading to the present name of the virus.1

**EPIDEMIOLOGY**

EBV is a widespread agent of low contagiousness, contracted by intimate contact (eg, kissing) between a susceptible person and an asymptomatic shedder. By adulthood, 90% to 95% of most populations worldwide have antibodies to EBV.1 In the United States, there is biphasic seroconversion; the first wave of infection occurs before age 5 years, usually manifesting as a subclinical infection, and the second wave occurs midway during the second decade of life, manifesting as clinical infectious mononucleosis. Lower socioeconomic groups have a higher prevalence of antibodies at a younger age.

EBV persists in the oropharynx of patients with mononucleosis for as long as 18 months after recovery from the illness.1 The virus can be cultured from throat washings of 10% to 20% of normal healthy adults and 50% of patients who have undergone organ transplantation or have HIV infection (or other immunocompromising conditions).2

**BIOLOGY**

Receptors for EBV exist on B lymphocytes and nasopharyngeal epithelial cells.2 The EBV receptor has been further identified as the receptor for the “d” region of the third component of complement (C3d receptor CD21).1 After attachment to the receptor, the virus gains entry into B lymphocytes, and Epstein-Barr nuclear antigen appears in nuclei of infected cells. Viral DNA synthesis is initiated, with viral DNA either incorporated into host DNA or remaining in nonintegrated episomes; the latter form is most common. On activation, a cascade of events ensues, with production of early antigen (EA) products and late genes, including viral capsid antigens (VCAs). The virus then enters a lytic cycle, resulting in production of progeny virions and destruction of the host cell. After infection, B lymphocytes capable of continuous in vitro cultivation are termed transformed.1

**PATHOGENESIS**

EBV is most commonly acquired via the oropharynx, where it infects B lymphocytes within the lymphoid tissue of the pharynx. During the 30- to 50-day incubation period from infection to clinical illness, viral replication and dissemination occurs throughout the lymphoreticular system.

Non-EBV-specific cell-mediated immune functions are depressed early in the course of illness, with an associated increase in the number of T lymphocytes of the suppressor subtype (ie, CD8+). The enlarged lymph nodes, spleen, and liver characteristic of infectious mononucleosis are associated with an increased infiltration of CD8+ cells. Salivary gland cells are also latently infected with EBV and have been alleged to play a role in malignant transformation in these cells. The B lymphocytes remain latently infected with EBV for the life of the host.

**CLINICAL MANIFESTATIONS**

**Infectious Mononucleosis**

**Clinical course.** Infectious mononucleosis, the most common clinical manifestation of EBV infection in adolescents and adults, is usually a self-limited illness, lasting from 2 to 3 weeks, with characteristic symptoms and signs (Table 1). The incubation period from exposure to clinical symptoms is approximately 30 days. Infectious mononucleosis presents with the triad of sore throat, lymphadenopathy, and fever,2 with fever usually peaking in the afternoon. In 5% of affected patients, a rash occurs that can be macular, petechial, scarlatiniform, urticarial, or erythema multiforme-like. Administration of the drug ampicillin can produce a pruritic, maculopapular eruption in 90% to 100% of affected patients, which may not appear until after discontinuation of the drug. There is usually tonsillar enlargement and cervical lymphadenopathy (most commonly posterior). Palatal petechiae at the junction of the hard and soft palates occur in 25% to 60% of patients with infectious mononucleosis, and splenomegaly can occur in another 52%. Splenomegaly is maximal at the beginning of the second week of illness and regresses over 7 to 10 days.1 Although fever typically lasts no more than 2 weeks, fatigue resolves more gradually.

There is considerable overlap in the presentation of infectious mononucleosis caused by EBV infection and the mononucleosis-like illness of acute retroviral syndrome. Clinicians should obtain a careful sexual history when adolescents and adults present with mononucleosis-like symptoms.

**Complications.** There are many potential complications of infectious mononucleosis.1–3 Hematologic complications include an autoimmune hemolytic anemia, which occurs in 0.5% to 3% of affected patients.1–3 Hemolytic anemia generally subsides over 1 to 2 months. Most hematologic complications are mediated by antibodies with anti-I specificity. Thrombocytopenia and neutropenia can also occur.

A life-threatening complication in patients with infectious mononucleosis is splenic rupture. Lymphocytic
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infiltration of the splenic capsule, coupled with rapid enlargement of the spleen, predisposes to rupture. The risk is highest in the second or third week of illness and must be strongly considered when abdominal pain occurs. Prompt splenectomy is the treatment of choice. Preventive measures include having patients avoid contact sports, treating constipation, and using caution when palpating the spleen.

Neurologic complications occur in fewer than 1% of patients with infectious mononucleosis; encephalitis is usually manifested as cerebellitis and generally has a complete recovery. Hepatic complications are more common; self-limited elevations of hepatocellular enzyme levels occur in 80% to 90% of cases. Cardiac or pulmonary complications of infectious mononucleosis are rare. Despite these potential complications, death from EBV infection is rare.

Chronic Persistent EBV Infection

Chronic persistent EBV infection (ie, chronic infectious mononucleosis) is different from the more common chronic fatigue syndrome. In those rare affected patients with objective organ dysfunction (eg, fever, lymphadenopathy, hepatosplenomegaly, pulmonary involvement, pancytopenia, ophthalmologic or neurologic abnormalities) associated with markedly abnor-

Table 1. Common Symptoms and Signs in Patients with Infectious Mononucleosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients Affected (%)</th>
<th>Variable</th>
<th>Patients Affected (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Sore throat 87</td>
<td>Signs</td>
<td>Lymphadenopathy 94</td>
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<tr>
<td></td>
<td>Malaise 57</td>
<td></td>
<td>Pharyngitis 84</td>
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<tr>
<td></td>
<td>Headache 51</td>
<td></td>
<td>Fever 76</td>
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<tr>
<td></td>
<td>Anorexia 21</td>
<td></td>
<td>Splenomegaly 52</td>
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<tr>
<td></td>
<td>Myalgias 20</td>
<td></td>
<td>Hepatomegaly 12</td>
</tr>
<tr>
<td></td>
<td>Chills 16</td>
<td></td>
<td>Palatal enanthem 11</td>
</tr>
<tr>
<td></td>
<td>Nausea 12</td>
<td></td>
<td>Rash 10</td>
</tr>
<tr>
<td></td>
<td>Abdominal discomfort 9</td>
<td></td>
<td>Jaundice 9</td>
</tr>
<tr>
<td></td>
<td>Cough 5</td>
<td></td>
<td>Vomiting 5</td>
</tr>
<tr>
<td></td>
<td>Arthralgias 2</td>
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-associated EBV serologies, it is sometimes difficult to discern whether active EBV infection has caused immune impairment or whether active EBV infection persists because of existing immunodeficiency.2

Associated Malignant Disorders

EBV is associated with African Burkitt’s lymphoma and most cases of nasopharyngeal carcinoma. EBV-related lymphoproliferative syndromes have been observed in patients who have received kidney, renal, or bone marrow transplants. Involvement may be confined to the lymph nodes, liver, spleen, and bone marrow or, more often, may present as extranodal disease. Histologically, a lymphoproliferative disorder can show hyperplasia or frank lymphoma, mostly of B-cell origin and commonly monoclonal. EBV is associated with lymphomas of the central nervous system (CNS) in patients with AIDS and is also the cause of the oral hairy leukoplakia (a benign exophytic growth of epithelial cells of the tongue and buccal mucosa) seen in AIDS patients and other severely immunocompromised individuals.2

DIAGNOSIS

Mononuclear lymphocytosis is found in 70% of patients with infectious mononucleosis, peaking in the second or third week of the disease course when monocytes and lymphocytes account for 60% to 70% of the total leukocyte count of 12–18 × 10³/mm³. Atypical lymphocytes are the hallmark of this infection, accounting for approximately 30% of the differential.1 Other laboratory findings include mild neutropenia, thrombocytopenia, abnormal results on liver function testing (with serum aminotransferase levels 2–3 times the upper limits of normal), and the presence of cryoglobulins (in as many as 90% of infected persons). Heterophilic antibodies are present in 90% of patients with infectious mononucleosis resulting from EBV infection and are detected as sheep and horse erythrocyte agglutinins and beef erythrocyte hemolysins.1 They are a heterogeneous group of predominantly IgM antibodies, and their role in the pathogenesis of or recovery from the illness remains unclear. A number of other antibodies can also be detected, including antibodies to platelets, neutrophils, lymphocytes, nuclear antigens, and ampicillin. EBV-specific antibodies are useful in confirming heterophile-negative and atypical cases of infectious mononucleosis. Antibodies to VCA arise early in the course of illness; a positive VCA-IgM titer is virtually diagnostic of acute EBV infection (Figure 1). Serologic responses of patients with EBV-associated diseases are presented in Table 2. Because
both healthy persons and those with unrelated illnesses intermittently shed EBV, viral culture is not a useful part of routine diagnostic evaluation.

Diagnosis of a lymphoproliferative disorder is based on histopathology, immunophenotyping, and detection of EBV DNA by DNA hybridization of tumor cells.

TREATMENT

Therapy for patients with infectious mononucleosis is largely supportive. Although the use of corticosteroids remains controversial for uncomplicated cases, these drugs have been associated with decreased fever and hastening of symptom resolution. Corticosteroids are generally indicated for the following complications of infectious mononucleosis: impending airway obstruction, severe thrombocytopenia, hemolytic anemia, CNS involvement, myocarditis, and pericarditis. Prednisone is generally initiated at a daily dose of 60 to 80 mg and tapered over 1 to 2 weeks.1 Antiviral therapy has been insufficiently studied in patients with infectious mononucleosis, but thus far no clear clinical benefit has been documented with administration of acyclovir. Viremia is present for 6 months after recovery, so blood donation should be postponed until after this time.

Although there is no definitive evidence showing a benefit of acyclovir administration in patients with an EBV lymphoproliferative disorder who have undergone organ transplantation, intravenous administration of acyclovir should be considered for these patients. The major goal of treatment in such cases should be to reduce or stop immunosuppression. More innovative approaches to the treatment of EBV-associated malignant disorders include the use of tumor-directed monoclonal antibodies and EBV-specific cytotoxic T cells.1 In summary, the indications for the clinical use of antiviral agents in the treatment of EBV infection remain relatively limited.

FURTHER DISCUSSION OF PATIENT 1

• How can the diagnosis be established for patient 1?
• What is the appropriate management for patient 1?

Patient 1’s history and physical examination results are consistent with acute infectious mononucleosis. Testing to determine the presence of heterophilic antibodies should be performed, because results will be positive in 90% of individuals with EBV-associated mononucleosis. Sexual history also should be obtained, given the clinical overlap between infectious mononucleosis and the syndrome of acute retroviral infection (assessed by obtaining an HIV viral load). If EBV infection is confirmed, supportive management is indicated. Moreover, the patient should be advised to abstain from playing soccer until his splenomegaly resolves, most likely in 7 to 10 days.

CYTOMEGALOVIRUS

HISTORICAL PERSPECTIVE

Beginning in the latter part of the nineteenth century, a previously unremarked infection of stillborn and deceased infants was observed; this infection, which typically involved the salivary glands and other organs, was characterized by large cytoplasmic inclusions.1 The causative agent of the infection was isolated in tissue culture in the 1950s, and its name was changed from salivary gland virus to CMV.2 Not until 1965 was the first case of CMV mononucleosis in an otherwise healthy adult described; it was reported to occur sporadically and after blood transfusions.5,6

EPIDEMIOLOGY

CMV infection is widespread and usually inapparent. The seroprevalence reaches 60% to 70% in urban US cities and nearly 100% in some parts of Africa.5 A biphasic incidence of infection occurs, with infections peaking first in the perinatal and childhood years and then again in the reproductive years.
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PATHOGENESIS

CMV infects children in 4 primary ways: (1) intrauterine infection, (2) infection during delivery, (3) transmission of infection via breast-feeding, and (4) transmission of infection via contact with other children within the family or daycare setting (occurring through close contact with virus-containing urine or saliva). The risk for infection from blood transfusion is less than 2.7% per unit of blood, a risk that is reduced even further by screening blood and eliminating seropositive donors.

Sexual transmission occurs via viral shedding in healthy infected adults, either from semen or from the cervix. CMV is found in urine, saliva, and blood for months after acute infection in healthy hosts or in chronically immunosuppressed patients. The frequency of colonization of the cervix correlates with a greater number of sex partners and a younger age at first intercourse, suggesting either that the cervix is reinfected or that carriage established at an early age persists. Semen carriage correlates with younger age, passive anal sex, and large number of sex partners.

BIOLOGY

CMV, like all HHVs, has the ability to establish latent infection in a host after recovery from acute infection. Polymorphonuclear cells, T lymphocytes, endothelial vascular tissue, renal epithelial cells, and salivary glands can all harbor the virus in a nonreplicating or slowly replicating form. Activation from this latent state can occur after immunosuppression, another illness, or use of immunosuppressive drugs. Clinical CMV disease can result from either primary or secondary infection, and infants and adults can be infected with multiple strains.

The CMV genome is a linear double-stranded DNA molecule that has been completely sequenced, although the protein products and their functions are still being identified. CMV contains many genes that encode proteins involved in the down-regulation of the host immune system as a way of evading control of the virus by the immune system. The pp65 antigen of CMV is useful for diagnosis, because it can be readily detected in infected cells of patients by immunofluorescence, immunoperoxidase, and other methods. CMV is not closely linked to any tumor.

CLINICAL MANIFESTATIONS

Perinatal Infection

Perinatal infection usually is diagnosed in infants who did not show evidence of infection at birth but become viruric at age 4 to 8 weeks. These children are usually asymptomatic and have no late deleterious effects, but subtle prolonged effects on hearing and intelligence have been reported. The illness can resemble infectious mononucleosis, but serious disease also can occur, particularly in premature infants. These premature infants sometimes have prolonged respiratory diseases, such as pharyngitis, bronchitis, pneumonia, and croup.

Table 2. Serologic Responses of Patients with Epstein-Barr Virus–Associated Diseases

<table>
<thead>
<tr>
<th>Condition</th>
<th>Anti-VCA</th>
<th>Anti-EA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IgM</td>
<td>IgG</td>
</tr>
<tr>
<td>Uninfected</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Infectious mononucleosis</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Convalescent</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Past infection</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Chronic active infection</td>
<td>–</td>
<td>+++</td>
</tr>
<tr>
<td>Posttransplant lymphoproliferative disease</td>
<td>–</td>
<td>++</td>
</tr>
<tr>
<td>Burkitt’s lymphoma</td>
<td>–</td>
<td>+++</td>
</tr>
<tr>
<td>Nasopharyngeal carcinoma</td>
<td>–</td>
<td>+++</td>
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</tbody>
</table>

Anti-EA = antibody to the Epstein-Barr early antigen; Anti-EBNA = antibody to the Epstein-Barr nuclear antigen; Anti-VCA = antibody to the Epstein-Barr viral capsid antigen; – = no antibodies detected; ± = variable presence of antibodies detected; + = low titers of antibodies present; ++ = moderate titers of antibodies present; +++ = high titers of antibodies present.

Congenital Infection

Congenital infection occurs less frequently than does perinatal infection but is associated with more serious syndromes. Diagnosis is suggested by evidence of viruria within the first week after birth. Most cases occur with primiparous mothers who contract primary infection during pregnancy; in the children of such mothers, there is a 55% intrauterine infection rate. Congenital infection can also occur in infants of mothers who are immune to CMV infection, but these infants are generally asymptomatic because of the immunity of the mother.5 Symptoms occur in fewer than one fourth of congenitally infected children overall.

Congenital cytomegalic inclusion disease is characterized by jaundice, hepatosplenomegaly, petechial rash, and multiple organ involvement. Microcephaly, motor disability, chorioretinitis, and cerebral calcifications are also seen.1 Involvement of the CNS, inner ear, and choroid of the eye are unique to congenital infection. The onset of lethargy, respiratory distress, and seizures immediately after birth herald this infection. Hemorrhagic phenomena, jaundice, and hepatosplenomegaly may subside, whereas CNS manifestations are less likely to resolve.5

CMV-Related Mononucleosis

CMV-related mononucleosis is clinically similar to EBV-related mononucleosis but is heterophile negative.7–9 Estimates suggest that 21% of infectious mononucleosis is caused by acute CMV infection.5 CMV-induced infectious mononucleosis is described as being more systemic in nature than is the EBV-associated form of the disease; fever is the predominating symptom, with lymphadenopathy and splenomegaly occurring less commonly and pharyngitis and tonsillitis occurring only rarely.7 Mild maculopapular and rubelliform rashes also can occur. Liver function abnormalities are typical. Other laboratory abnormalities include the appearance of cold agglutinins, rheumatoid factor, mixed cryoglobulinemia, antinuclear antibodies, and anticomplementary activity.5

Transmission occurs via intimate/sexual contact or blood transfusion. Complications include pneumonitis (generally a radiographic finding that clears), hepatitis (frequently present), granulomatous hepatitis, and Guillain-Barré syndrome (a well-recognized complication). More rarely, meningoencephalitis, myocarditis, thrombocytopenia, and hemolytic anemia can occur.5

CMV Infection in Immunosuppressed Patients

Transplantation. All major organ transplantations are associated with an increased risk for CMV infection, including kidney, liver, heart, heart-lung, and bone marrow transplants.10 Most commonly, a febrile mononucleosis termed CMV syndrome occurs, which is defined as CMV infection accompanied by an otherwise unexplained fever lasting 48 hours, malaise, and a fall in neutrophil count over 3 consecutive days.9 Increased risk is associated with seronegative recipients of seropositive donor organs or blood products and with use of immunosuppressive drugs in transplant recipients. Secondary infection after activation of latent virus is also a possible source of infection in any seropositive recipient, although it is less commonly associated with fever.9 Interstitial pneumonia, the most severe and lethal form of CMV diseases in adults, occurs in the first 120 days after bone marrow transplantation and is associated with delayed engraftment in the recipients. Moreover, CMV infection in lung transplant patients is a major cause of mortality, involving the transplanted lung preferentially. Additionally, graft-versus-host disease often occurs with CMV diseases, particularly if the transplant recipient requires extensive immunosuppression for management. Finally, CMV occurring after organ transplantation can have the indirect effect of increasing the incidence of fungal and bacterial infections.

AIDS. With progressive immunosuppression, CMV activity increases, with the highest risk associated with CD4+ cell counts of 50/mm^3^ or less. Viremia is already present in many patients with AIDS and so is not useful for determining active infection. Retinitis occurs as the most common manifestation of CMV infection in patients with AIDS, but disease may involve nearly any organ, including the lung, gastrointestinal tract, pancreas, biliary tract, and CNS. The incidence of CMV end-organ disease has decreased by more than 80% with the advent of highly active antiretroviral treatment (HAART), the most likely reason being an improvement in CMV-specific immune responses with treatment.5 A screening retinal examination every 6 months is recommended for infected individuals with CD4+ cells counts of 50/mm^3^ or less.

For patients receiving HAART, maintenance treatment of CMV retinitis can be safely discontinued without relapse in those who have demonstrated a sustained response to antiretroviral therapy, evidenced by an undetectable viral load and CD4+ cells counts greater than 150 cells/mm^3^ for 3 months.11 However, immune recovery vitreitis has been reported in patients whose immune function has improved significantly with HAART, so continuation of CMV therapy may be protective.

CMV-related pneumonia. CMV-related pneumonia ranges from asymptomatic shedding to a rapidly fatal process in recipients of bone marrow transplants. Distribution is usually interstitial on chest radiographs.
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Hepatitis. CMV hepatitis, characterized by prolonged fever, elevated bilirubinemia, and elevated liver enzyme activity, is of greatest concern in liver transplant recipients. In these patients, liver biopsy is required to distinguish CMV hepatitis from organ rejection.

Gastrointestinal infection. CMV infection of the gastrointestinal tract was frequent in patients with AIDS before the era of HAART. CMV can infect any part of the gastrointestinal tract, from the esophagus to the rectum. Tissue biopsy is required for diagnosis. Other CMV infections of the gastrointestinal system include pancreatitis, acalculous cholecystitis, papillary stenosis, and sclerosing cholangitis. With esophagitis, patients initially have pain and difficulty swallowing, and shallow ulcers are evident on endoscopy.

Patients with AIDS may have explosive watery diarrhea as a result of CMV colitis. Fever is common, and bloody diarrhea may be present. Diagnosis of CMV colitis is made by sigmoidoscopy, which reveals plaque-like pseudomembranes, numerous erosions, and serpiginous ulcers.5

Gastrointestinal CMV is typically treated with intravenous administration of ganciclovir or foscarnet over a 2 to 3 week period. Although relapses are common, occurring in as many as 50% of patients, they often do not occur until 6 months (or more) after initial infection; thus, retreatment may be more appropriate than maintenance therapy.

Retinitis. As previously implied, retinitis is most common in patients with AIDS. It initially involves blurred or decreased vision or scotoma. Visual impairment is usually irreversible. White granular necrotic patches superimposed with patches of flame-shaped intraretinal hemorrhages can be seen on indirect retinal examination by a specialist familiar with the disease. Retinitis rarely occurs in patients who have received an organ transplant.

Neurologic involvement. Approximately half of symptomatic congenital CMV infections will have a degree of CNS involvement. Inapparent infections can manifest as late neurologic sequelae, the most serious of which is neurosensory deafness.

Besides retinitis, the most common neurologic manifestations of CMV infection in patients with AIDS include encephalopathy or polyradiculopathy. Encephalitis presents with acute onset of confusion, lethargy, nystagmus, ataxia, cranial nerve palsies, and subacute progression to coma and death. Atrophy, enlarged ventricles, and periventricular enhancement are detected on magnetic resonance imaging scans enhanced with gadolinium. Cerebrospinal fluid of affected patients generally has relatively few leukocytes, a low glucose level, and an elevated protein level. No benefit resulting from antiviral therapy has been documented.

Polyradiculopathy has a characteristic onset of ascending weakness in the lower extremities associated with a loss of deep tendon reflexes and ultimately loss of bowel and bladder control. The syndrome frequently begins as low back pain with a radicular or perianal radiation followed in 1 to 6 weeks by a progressive flaccid paralysis. Analysis of cerebrospinal fluid obtained on lumbar puncture reveals a characteristic picture of polymorphonuclear cells, a mildly elevated protein level, and modest hypoglycorrhachia.5 Early treatment is essential to avoid permanent paraplegia. Although ganciclovir and foscarnet have each been used as single therapy for CMV polyradiculopathy, the current favored treatment is early therapy with combination ganciclovir and foscarnet5 (although no vigorous clinical trials to document improved benefit over monotherapy have been published).

Involvement of the endocrine system. CMV-associated adrenalitis occurs most commonly in patients with AIDS.

DIAGNOSIS

Diagnosis of CMV infectious mononucleosis by serology requires acute and convalescent titers to document a rise in IgG or a conversion from negative to positive. Using IgM is generally not reliable because of possible false-positive and false-negative results, except in cases of congenital infection in which a positive finding of IgM in cord blood is considered definitive.

Viral culture is facilitated by detection of immediate EAs in shell vial cultures at 48 hours. However, because of asymptomatic shedding of virus, culture generally supplies only supportive information. Quantitative detection of antigenemia (eg, pp65 antigen) in circulating neutrophils has been useful for diagnosis in patients who have undergone organ transplantation and in those who have AIDS. Polymerase chain reaction (PCR) detection of immediate EA is increasingly available commercially. Qualitative PCR can detect small amounts of CMV DNA in many body fluids, including the cerebrospinal fluid of patients with CMV encephalitis or CMV polyradiculopathy5; definitive diagnosis requires histopathologic examination that detects inclusion-bearing cells.

Quantitative PCR has been shown to predict disease activity in patients with AIDS and has revolutionized the approach to management of CMV disease in the liver, kidney, and bone marrow of transplant recipients. The approach, termed pre-emptive therapy, detects CMV DNA in plasma before end-organ disease develops and employs antiviral therapy to lower CMV DNA levels.5
PHARMACOLOGIC TREATMENT

Ganciclovir

Ganciclovir is a synthetic purine nucleoside analogue of guanine that is 10 to 100 times more potent against CMV than is acyclovir. Its main potential adverse effect is neutropenia. Ganciclovir delays progression of retinitis in patients with AIDS by approximately 40 days. It is used for induction therapy (5 mg/kg body weight twice daily intravenously for 14 to 21 days) and maintenance therapy (5 mg/kg daily intravenously or 1 g 3 times daily orally). In patients who have undergone bone marrow transplantation, ganciclovir is used with CMV immunoglobulin to treat CMV pneumonia. However, a uniform prophylaxis regimen for bone marrow transplant patients does not yet exist, so treatment varies from medical center to medical center. Orally administered ganciclovir can be used alone as maintenance therapy in patients with AIDS who develop CMV retinitis but is less effective than the intravenously administered formulation. Primary prophylaxis for AIDS patients remains unproved.

Ganciclovir is available as an intraocular implant for selected cases of unilateral retinitis, in combination with orally administered ganciclovir. The implant has been more effective than intravenously administered ganciclovir in the treated eye but is not effective in the other eye or other organs. The ocular implant usually lasts for 5 to 8 months.

Foscarnet

Foscarnet is a pyrophosphate that inhibits viral DNA polymerase of herpesviruses and HIV reverse transcriptase. Active against most ganciclovir-resistant CMV strains, foscarnet has an efficacy similar to that of ganciclovir in cases of CMV retinitis; it is administered intravenously at 90 mg/kg daily in two divided doses for 14 days of induction, followed by a maintenance dose of 90 to 120 mg/kg daily. Its use has been associated with longer survival in AIDS patients. Major adverse effects include nephrotoxicity, electrolyte imbalance (including hypocalcemia, hypomagnesemia, and hypophosphatemia), seizures, and nausea. Metabolic toxicity can be effectively managed by carefully monitoring serum creatinine levels and replacing magnesium, calcium, and phosphate losses.

Cidofovir

Cidofovir is a nucleotide analogue that is active against CMV, EBV, herpes simplex virus, and varicella-zoster virus. Phosphorylation of cidofovir to its active form is not dependent on viral enzymes, so development of resistance may be slow. Acyclovir- or ganciclovir-resistant strains of CMV often remain susceptible to cidofovir. The slow elimination half-life (17–65 hours) of its active intracellular metabolite permits prolonged intervals between doses and eliminates the need for permanent intravenous access. The drug is given weekly for 2 weeks for induction and then is administered once every 2 weeks.

Adverse effects include nephrotoxicity, ocular hypotony, neutropenia, and metabolic acidosis. Cidofovir is contraindicated in patients with a serum creatinine level greater than 1.5 mg/dL, a urine creatinine clearance of 55 mL/min or less, or proteinuria (urine protein level of 100 mg/dL or more) and in patients taking other nephrotoxic agents, including nonsteroidal anti-inflammatory drugs. To decrease the risk of nephrotoxicity, intravenous administration of saline and oral administration of probenecid are appropriate before and after each dose. However, adverse reactions to probenecid are common and may prevent further use of cidofovir. Because of nephrotoxicity, intravenously administered cidofovir is generally reserved for individuals with CMV retinitis who have failed first-line regimens with ganciclovir or foscarnet.

Newer Agents

Valganciclovir, the oral prodrug of ganciclovir, was recently approved by the Food and Drug Administration for the treatment of CMV retinitis in AIDS patients. The bioavailability of ganciclovir from this new drug is approximately 60%. Valganciclovir (available in 450 mg tablets) is administered in 900 mg doses twice daily for 21 days for induction and in a 900 mg dose once daily for maintenance. This recently approved drug may have an efficacy comparable to that of intravenously administered ganciclovir without the inconvenience and risk of catheter-related complications.

Finally, fomivirsen is an antisense inhibitor of CMV used for direct injection into intravitreal fluid for treatment of CMV retinitis.

PREVENTION OF CMV INFECTION IN ORGAN TRANSPLANT RECIPIENTS

Routine prevention of CMV infection in cases of organ transplantation includes transfusion of CMV-seronegative or filtered blood products to CMV-seronegative immunosuppressed patients. CMV hyperimmune globulin given in the first 4 months after renal and liver transplantation provides significant protection for CMV-seronegative recipients of CMV-seropositive organs.

A protective effect of acyclovir has been shown in some, but not all, studies. According to 1 report, ganciclovir prophylaxis reduced CMV disease more effectively but was complicated by neutropenia. Determining the CMV viral load and using antigen detection
are new techniques that allow for pre-emptive therapy, which is changing the clinical management of CMV infection in the setting of organ transplantation as results of further studies become available.

**FURTHER DISCUSSION OF PATIENT 2**

- **What is the appropriate diagnostic work-up for patient 2?**

  Patient 2 may have CMV retinitis, which presents with blurred or decreased vision, scotomas, and floaters. The patient needs urgent referral to a retinal specialist for indirect retinal examination to detect changes indicative of this disease. Testing of peripheral blood for CMV antigen pp65 or PCR detection of immediate EA in serum can provide supportive evidence of CMV infection but is not required for management. If he has hemorrhagic and exudative changes (the so-called “ketchup and cottage cheese” appearance) on retinal examination, he should immediately begin receiving antiviral therapy (usually, intravenous induction therapy with ganciclovir for 2 to 3 weeks); his leukocyte count should be carefully monitored while he receives this therapy. Once his retinal changes stabilize and induction is completed, assuming the opposite eye remains unaffected, the option of a ganciclovir intraocular implant (in combination with maintenance therapy with orally administered ganciclovir) may be considered. The implant will need to be replaced approximately twice yearly, and maintenance will need to be continued indefinitely, unless a sustained virologic and immunologic response to HAART is achieved. Alternatively, orally administered valganciclovir 900 mg once daily could be used for maintenance therapy.

**HUMAN HERPESVIRUSES 6 AND 7**

**HHV-6**

**General Considerations**

As many as 70% of infants acquire HHV-6 in the second 6 months of life. Overall, primary infection with HHV-6 is a major cause of acute febrile illness in young children. Two subtypes of HHV-6 exist, A and B, with nearly all cases of primary infection caused by subtype B. Infection persists for life, and virus can be isolated from the saliva of most adults. The virus can infect many cell types but primarily is found in CD4+ T lymphocytes.

HHV-6 is the cause of exanthem subitum or roseola (sixth disease). Roseola is a benign illness of infants and young children. Symptoms consist of 3 to 5 days of fever, with occasional respiratory symptoms and cervical lymphadenopathy. A maculopapular rash appears on the trunk and neck within 48 hours following defervescence of fever. Occasionally, fever can occur without the rash. The course may be complicated by febrile seizures and, rarely, by meningoitis and encephalitis. The association between HHV-6 infection and febrile seizures is particularly pronounced in children age 12 to 15 months; in 1 study, 36% of children in this age range with HHV-6 infection and fever had convulsions, compared with only 13% of children with febrile illnesses not related to HHV-6 infection.

**HHV-6 Infection in Adults**

Infection with HHV-6 in adults causes a range of illnesses, from a mononucleosis-like illness to pneumonitis and fulminant hepatitis. HHV-6 may also be an important pathogen in transplant recipients.

Approximately 30% to 45% of recipients of bone marrow transplants develop HHV-6–associated viremia within the first several weeks of transplantation, most often manifested as fever and rash, a low incidence of other disease manifestations has also been reported, including bone marrow suppression, pneumonitis, encephalitis, and graft-versus-host disease. Although reactivation of asymptomatic HHV-6 infection predominates in the post–bone marrow transplantation setting, the pathogenic significance of HHV-6 reactivation in recipients of bone marrow transplants remains uncertain.

Moreover, up to 66% of solid-organ transplant recipients have HHV-6 reactivation or reinfection, as measured by viral isolation or PCR analysis. Reactivation most commonly occurs after treatment for organ rejection with either muromonab-CD3 (OKT3) or antithymocyte globulin and is probably related to the significant degree of immunosuppression associated with both products. The reported association between HHV-6 reactivation and graft rejection remains uncertain. HHV-6 reactivation does, however, lead to subsequent reactivation of CMV.

Patients with HIV-1 infection also exhibit frequent reactivation of HHV-6. In most HIV-1 positive adults, HHV-6 reactivation is thought to have minimal effect on progression of HIV-1 infection. In contrast, in infants with vertically acquired HIV-1 infection, primary HHV-6 infection has been associated with more rapid progression of HIV-1 infection during the first year of life. More research is needed to understand fully the possible role of HHV-6 infection in the progression of HIV-1 infection.
Finally, the neurotropism of HHV-6 is of particular interest. Its possible role in exacerbations of multiple sclerosis is being evaluated.\(^{27}\)

**Diagnosis**

Diagnosis of HHV-6 infection requires development of a fourfold or greater increase in anti–HHV-6 IgG titers. Anti–HHV-6 IgM testing is not reliable. Likewise, a positive viral culture does not establish causation in an immunocompetent host; the virus can be isolated from blood and saliva of healthy persons. However, in an immunocompromised transplant recipient with clinical evidence of disease related to HHV-6, viral culture or DNA detection by PCR of blood or tissue is warranted, although the role of these tests is still being defined.

**HHV-7**

HHV-7 is very similar to HHV-6 and also highly prevalent.\(^{21}\) Although the clinical manifestations and implications of HHV-7 infection have yet to be clarified, it may cause up to a third of cases of exanthem subitum and is the cause of pityriasis rosea.

Specific tests for HHV-7 are currently only research tools and are not commercially available. The commercially available HHV-6 test for IgG exhibits cross-reactivity with HHV-7.

**TREATMENT OF HHV-6 AND HHV-7**

As infection with HHV-6 and HHV-7 is generally a benign, self-limited infection, only symptomatic therapy is required.\(^{22}\) These viruses are sensitive to foscarnet and cidofovir,\(^{21}\) which are options as treatment in transplant recipients. However, routine monitoring for these viruses after organ transplantation remains experimental, and no controlled trials of antiviral therapy in this setting have been completed.\(^{26}\)

**FURTHER DISCUSSION OF PATIENT 3**

- **What is the most likely diagnosis for patient 3?**

  Given her signs, symptoms, and exposure to exanthema subitum (sixth disease), Patient 3 most likely is infected with HHV-6. HHV-6 infection is a major precipitant of seizures in infants because of the high fever infection provokes, as well as the neurotropism of the virus. Viral meningitis and encephalitis occur only rarely. Her fever should be controlled by administration of acetaminophen or ibuprofen to prevent further seizures, and other supportive measures such as fluid and electrolyte management should be provided. The fever of roseola (exanthem subitum or sixth disease) typically abates after 5 days and is followed (within 48 hours) by the appearance of rash. Diagnosis can be retrospectively confirmed by acute and convalescent HHV-6 serology or by PCR of cerebrospinal fluid.

**REFERENCES**


