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Update on herpesvirus infections

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Of the 80 known herpesviruses, 8 of them are known to cause infections in humans, including herpes simplex virus (HSV) 1 and 2, varicella zoster virus (VZV), cytomegalovirus (CMV), Epstein–Barr virus (EBV), human herpesvirus 6 (HHV-6), human herpesvirus 7 (HHV-7), and human herpesvirus 8 (HHV-8). The following are characteristics common to the members of the herpesvirus family:

1. They contain four layers: an inner core of double-stranded DNA, a protein capsid, the tegument, and a lipid envelope containing glycoproteins derived from the nuclear membrane of host cells [1].
2. They cause a primary infection when the patient initially contacts the virus and remain latent within the nuclei of specific cells for the life of the individual. The site of latency differs among the herpesviruses, with HSV1, HSV2, and VZV remaining latent in the sensory nerve ganglia; CMV in lymphocytes and possibly salivary gland tissue; EBV in B lymphocytes and salivary gland tissue; and HHV-6 and HHV-7 in CD4 lymphocytes. HHV-8 also remains latent; however, the exact site of latency is still unknown, although it is most likely associated with B lymphocytes circulating in the hematopoietic system.
3. After reactivation, herpesviruses can cause localized symptomatic or asymptomatic recurrent infections.
4. They are transmitted from host to host by direct contact with saliva or genital secretions. HHV-8 may be transmitted by way of organ transplantation [2].
5. They are shed in the saliva of asymptomatic hosts who act as constant reservoirs for new primary infections in previously uninfected individuals.

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6. Herpesviruses are known to transform cells in tissue culture. EBV has been associated with malignancies in humans, such as nasopharyngeal carcinoma and B-cell lymphomas. Recently, there have been reports of other malignancies associated with EBV, including a nasal T-cell/natural killer cell lymphoma seen most commonly in Southeast Asia [3]. HHV-8 has been definitively linked to malignant processes such as Kaposi's Sarcoma (KS), to several lymphoproliferative disorders, and to Castleman's disease [2].

This article reviews the basic virology, clinical manifestations, and management of herpes infections.

HSV

HSV1 and HSV2 are the two major types of herpes simplex viruses. They can be distinguished on the basis of the distinct antibodies that are formed against each type of virus or by analysis of the nuclear DNA by restriction endonuclease analysis [4]. Classically, HSV1 causes a majority of cases of oral and pharyngeal infection, meningoencephalitis, and dermatitis above the waist; HSV2 is implicated in most genital and anal infections [1]. Depending on sexual practices, both types can cause primary or recurrent infections in the oral and/or genital area [1]. HSV infection of the finger (herpetic whitlow) develops after contact with infected saliva or bronchial secretions.

Primary herpes simplex infections

The incidence of primary infections with HSV1 increases after 6 months of age due to loss of anti-HSV antibodies acquired from the mother during gestation. The incidence of primary HSV1 infection reaches a peak between 2 and 3 years of age [4]. Primary HSV1 infections may still occur in adolescents and adults, with occasional cases being reported in patients over 60 years of age [5]. Incidence of primary HSV2 infection does not increase until sexual activity begins.

The incidence of primary herpes infections has been shown to vary according to socioeconomic group. In lower socioeconomic groups, 70% to 80% of the population have detectable antibodies to HSV by the second decade of life, indicating prior HSV infection, whereas in a group of middle-class individuals, only 20% to 40% of the patients of the same age have evidence of contact with HSV [4].

A significant percentage of primary herpes infections are subclinical or cause a pharyngitis difficult to distinguish from other upper respiratory viral infections. Symptomatic primary HSV disease is preceded or accompanied by generalized symptoms that may include fever, headache, malaise, nausea,

and vomiting. Lymphadenopathy may also be evident. In the oral cavity, vesicles and ulcers appear on the oral mucosa, and generalized acute marginal gingivitis occurs 1 to 2 days after the prodromal symptoms appear. Primary HSV in healthy children is a self-limiting disease, with fever disappearing in 3 or 4 days and oral lesions that heal in a week to 10 days.

Treatment of primary HSV infection is usually palliative. Milder cases can be managed by supportive care only, including maintenance of fluids, use of acetaminophen to reduce fever, use of topical anesthetics such as viscous lidocaine, or a mixture of liquid benadryl, milk of magnesia, and carafate (''magic mouthwash'') can be administered to decrease oral pain. If the patient presents to the clinician within 72 hours of onset of vesicle eruption, antiviral medication may be helpful in decreasing healing time of the lesions by inhibiting DNA replication in HSV-infected cells [6]. Acyclovir has been shown to decrease symptoms of primary HSV infection in children, including days of fever and viral shedding [7]. The recommended dose of acyclovir for treatment of primary HSV is 200 mg five times per day. Newer antiherpes drugs are now available including valacyclovir and famciclovir. The advantage of the newer drugs is increased bioavailability, allowing for effective treatment with fewer daily doses [8]. The recommended dose of valacyclovir to treat primary HSV is 1000 mg two times per day, whereas the recommended dose of famciclovir is 250 mg three times per day.

Recurrent HSV infection

Following resolution of a primary HSV infection, the virus migrates to the trigeminal nerve ganglion where it is capable of remaining in a latent state. Reactivation of virus may follow exposure to sunlight, exposure to cold, trauma, stress, or immunosuppression and cause a recurrent infection [9]. Recurrent herpes labialis (RHL) is the common form of recurrent oral HSV infection that appears on the vermillion border or skin of lip and is commonly referred to as a cold sore or a fever blister. Recurrent herpes infections in otherwise healthy patients should be treated symptomatically. Treatment of severe, painful, or deforming recurrent herpes may require systemic antiviral medications. The recommended dose of acyclovir is 200 mg five times per day or valacyclovir, 1000 mg once per day or famciclovir, 250 mg once per day. If an individual knows he or she will be in an environment likely to cause RHL, such as a skiing or beach vacation, a clinician may prescribe prophylactic antiviral medications. The recommended prophylactic dose of acyclovir is 400 mg twice per day or valacyclovir, 500 mg once per day or famciclovir, 250 mg once per day for the duration of the trip.

There have been studies published regarding the use of topical antiviral medications for treating RHL [10,11]. Topical penciclovir reduces the duration and pain of RHL by 1 to 2 days [12]. The recommended dosage of

topical penciclovir is application to the area every 2 hours for 4 days while awake. Acyclovir and n-docosanol cream, which is newly approved by the Food and Drug Administration, are also currently available. The benefit of applying these medications to RHL lesions seems to be limited and does not significantly decrease the duration of lesions [10]. Some clinicians advocate the use of suppressive doses of acyclovir to prevent severe, frequent, disfiguring recurrences of RHL.

Although most recurrent herpes infections occur on the lips and heavily keratinized mucosa of the palate and gingiva, recurrent intraoral herpes can occur on any intraoral mucosal surface and is seen most frequently in immunocompromised patients. Patients at high risk for severe recurrences are those receiving cancer chemotherapy or immunosuppressive drugs to prevent graft rejection after transplantation and patients with AIDS [1]. Recurrent HSV lesions in immunocompromised patients appear as progressively enlarging ulcers that may involve large portions of the labial, intraoral, genital, or rectal mucosa if left untreated [13]. These lesions occasionally disseminate, causing generalized infection; therefore, it is imperative for clinicians to rule out HSV as a cause of oral vesicles or ulcers in immunosuppressed individuals [1].

Immunosuppressed patients with HSV infection respond well to acyclovir administered orally or intravenously [14]. Occasional cases of acyclovir-resistant HSV have been reported and foscarnet, a newer antiviral drug, has been effective therapy for these patients [15]. Valacyclovir is contraindicated for use in immunosuppressed patients due to the potential risk of hemolytic uremic syndrome.

Recurrent HSV has been known to trigger episodes of erythema multiforme. HSV is presently believed to be the most common cause of recurring episodes of erythema multiforme in susceptible individuals who develop an immune response to HSV. Patients who get severe recurring erythema multiforme from HSV commonly receive prophylactic doses of antiviral medication to prevent recurrence. The recommended prophylaxis doses are the same for suppression of RHL.

Diagnosis

The majority of HSV infections are diagnosed clinically; however, laboratory tests may be necessary to diagnose atypical presentations of HSV infections. These tests should be used when evaluating immunocompromised patients with atypical lesions.

Virologic tests

The "gold standard" for virus identification and diagnosis is isolation in tissue culture. The goal of virus isolation is to observe cytopathic effects of

the cells inoculated with virus. Cytopathic effects are the degenerative changes that cells undergo when infected with virus. The rate at which cytopathic effects develop is dependent on the type of host cell, the type of virus, and the concentration of virus [16]. When viewed at high power by way of light microscopy, virally infected cells will demonstrate multinucleated giant cells, syncitium, and ballooning degeneration of nuclei.

A more expedient method of virus isolation is the shell-vial culture technique, which entails the inoculation of multiple vials with cell lines for the identification of viral pathogens from a clinical specimen. The critical advantage of shell-vial culture over conventional tube cell culture is the ability to identify the virus before viral replication in the host cell leads to cytopathic effects. Virus can be detected in 1 to 5 days compared with 1 to 4 weeks required by conventional cultures [16]. When HSV is isolated from lesions contaminated with saliva, positive HSV cultures may be caused by asymptomatic shedding of virus in a patient with a coincidental non-HSV lesion.

Cytology smears

A smear of epithelial cells taken at the base of a suspected lesion may be studied to determine whether epithelial cells show changes consistent with HSV infection. The most common stain used is Giemsa stain, however other stains used are Wright, methylene blue, Papanicolaou stain, or toluidine blue. Virally infected cells will demonstrate the same characteristics that are demonstrated by virologic testing. When a Papanicolaou stain has been performed, eosinophilic intranuclear viral inclusion bodies (Lipschutz or Cowdry type A) can be seen. Routine cytology smears cannot differentiate between HSV and VZV infection but are a useful diagnostic tool in determining whether there is a viral etiology to the disease process.

Immunomorphologic tests

The diagnosis of herpesvirus infections can be made more quickly and accurately by using immunomorphologic techniques [17]. Viral antigen detection in lesion material, by direct fluorescent assay, usually has a sensitivity of 80% to 90% [18]. In the direct fluorescent assay, the specimen is incubated with fluorescein isothiocyanate–labeled HSV type–specific monoclonal antibody [19]. The positively infected cells are fluorescent green when examined under a fluorescent microscope. This technique can be used for the rapid diagnosis of a clinical specimen, the identification of virus in tissue culture displaying cytopathic effects, and the typing of recovered HSV isolates from tissue culture [20]. Studies have concluded that the overall sensitivity of direct fluorescent assay techniques to detect HSV is 80%, the specificity is 98% to 100%, and the positive predictive value ranges from 90% to 100% [21,22].

Serologic tests

Serologic tests are completed to detect antibody formation in a patient's blood sample. They are useful in diagnosing a primary HSV infection; a fourfold or greater antibody rise in convalescent serum is required for the diagnosis of a primary infection. When serology is used in the diagnosis of suspected HSV infection, an acute specimen should be obtained within the initial 3 days of the infection and a convalescent specimen approximately 4 weeks later. Due to the delayed humoral response, antibodies are not present in the acute specimen but appear during convalescence, which may provide useful retrospective information but is of little help when managing a patient in the acute phase of illness. HSV serology is useful when attempting to detect patients who are susceptible to serious recurrent HSV infections during periods of profound immunosuppression [1]. This serologic test is particularly useful before solid organ transplantation when patients with a positive HSV serology may receive prophylactic antiviral therapy to prevent HSV reactivation and serious infection [1].

VZV

VZV causes both primary and recurrent infection and remains latent in neurons present in sensory ganglia [4]. VZV is responsible for two major clinical infections: the primary type is chickenpox (varicella) and the recurrent type is shingles (herpes zoster [HZ]).

Varicella

Chickenpox is characteristically a benign illness of children spread by direct contact with either the skin lesions or nasopharyngeal secretions of an infected individual [1]. The incubation period is 10 to 21 days, and patients are infectious for approximately 1 week after symptoms begin. The mortality rate for adults with chickenpox is 15 times greater than in children due to an increased incidence of encephalitis [1]. Other complications of chickenpox include pneumonitis and Reye's syndrome, a progressive encephalopathy that most frequently occurs in children who have been given aspirin during an acute varicella infection [23].

Skin lesions of chickenpox are characterized by maculopapular lesions that are intensely pruritic. The lesions rapidly develop into fluid-filled vesicles on an erythematous base. Oral lesions may be present that resemble vesicles/ulcers seen in primary HSV, but these lesions are not a particularly important symptomatic, diagnostic, or management problem [4].

Herpes zoster

After primary infection, VZV becomes latent in dorsal root or cranial nerve ganglia. In 0.3% to 0.5% of the population, the virus becomes

reactivated, causing HZ [1]. The nerves most commonly affected with HZ are C-3, T-5, L-1, and L-2. When HZ involves the trigeminal ganglion, the first division (ophthalmic or V_1) is most commonly involved, and eye involvement becomes a potentially serious complication. Consultation with an ophthalmologist is necessary in these cases.

The initial symptoms of HZ are pain, tenderness, and paresthesia along the course of the affected nerve. Three to 5 days later, unilateral vesicles appear on an inflamed base along the involved nerve. When the geniculate ganglion of the facial nerve is infected, characteristic signs include unilateral vesicles of the external ear and oral mucosa, as well as unilateral facial paralysis, a group of signs referred to as Ramsay-Hunt Syndrome [1]. HZ may also occasionally affect motor nerves.

Approximately 15% to 20% of the cases of HZ of the trigeminal nerves affect either the maxillary division (V_2) or mandibular division (V_3), leading to pain, unilateral facial lesions, and intraoral lesions along the course of the affected nerve [4]. Diagnosis of HZ is usually made based on characteristic clinical signs and symptoms. VZV may cause pain without lesions developing along the course of the nerve. This is called zoster sine herpete or zoster sine eruptione [4]. Atypical presentations may require laboratory testing for confirmation of VZV. These methods include viral cultures, cytology smears, immunomorphologic techniques, and serologic testing, as previously described.

Immunocompromised patients with HZ are at risk for developing life-threatening infections. In this group, HZ may cause large local lesions or disseminated infection. Oral HZ in immunosuppressed patients has been reported to cause necrosis of alveolar bone and exfoliation of teeth [4]. Disseminated infections among immunocompromised individuals may include widespread skin lesions, meningitis, encephalitis, VZV pneumonia, and hepatitis.

Antivirals such as acyclovir are effective in shortening the course of HZ, accelerating healing, and reducing acute pain [4]. The required dose of acyclovir used to treat HZ is 800 mg five times per day, four times greater than the effective dose for treating primary HSV. The recommended dose of valacyclovir is 1000 mg three times per day or famciclovir, 500 mg three times per day. These medications have been reported to be more effective than acyclovir for treating HZ [4].

Postherpetic neuralgia is a potential sequela of HZ resulting from scarring of the involved nerve during infection [1]. Postherpetic neuralgia is a painful, sometimes debilitating condition that can last months to years after the lesions are healed. The incidence of postherpetic neuralgia is increased in patients over 50 years, and use of valacyclovir or famcyclovir has been advocated to reduce its incidence and duration [24]. Some investigators report that the use of a short course of systemic corticosteroids decreases the incidence of postherpetic neuralgia, but the usefulness of this recommendation is disputed [1]. Other effective therapies for treatment of

postherpetic neuralgia are topical capsaicin, tricyclic antidepressants, and gabapentin [4].

CMV

CMV is a frequent cause of asymptomatic infection in humans and may cause significant clinical disease in immunosuppressed patients [25]. The virus is transmitted in several ways: (1) during birth by way of contact with CMV-positive vaginal secretions, (2) by way of breast milk, (3) by way of saliva in young children, (4) by way of contaminated blood transfusions or transplanted organs, and (5) by way of sexual transmission from semen or uterine secretions [1].

Neonates may develop cytomegalic inclusion disease, a congenital form of CMV infection. In its most severe form, this disease is associated with microcephaly, chorioretinitis, nerve deafness, hepatitis, hepatosplenomegaly, and thrombocytopenia [25]. Salivary gland enlargement is a common finding in this disease [1]. The majority of congenitally affected neonates, however, are asymptomatic at birth and only 5% to 15% of these subsequently develop sequelae, the most common being isolated sensorineuronal deafness [26].

In healthy children and adults, primary CMV infection is usually asymptomatic. Infection with CMV can produce a heterophil-negative mononucleosis-like disease that may be clinically indistinguishable from infectious mononucleosis caused by EBV infection. This primary CMV infection results from either blood transfusions or sexual contact in a previously seronegative person [1]. Clinical symptoms include fever, myalgia, cervical lymphadenopathy, and mild hepatitis. Tonsillopharyngitis is much less common than in primary EBV infection, and lymphadenopathy and splenic enlargement are less prominent features [25]. Complications of primary CMV infection may include myocarditis, pneumonitis, and aseptic meningitis.

CMV infection may produce serious disease and death in immunosuppressed patients who have deficiencies of cell-mediated immunity. Patients at risk for developing life-threatening CMV infections are solid organ and bone marrow transplant recipients and patients with HIV infection. Solid organ transplant recipients have a 3 to 5 times greater risk of developing CMV disease if they are seronegative and receive an organ from a seropositive donor; in addition, the disease can be much more severe [25]. Patients who are seropositive at the time of transplantation are susceptible to recurrent infection caused by reactivation of latent CMV [1]. Many institutions attempt to match seronegative donors to seronegative recipients; however, due to the limited number of available donor organs, this is not often achieved. CMV disease is a major problem in allogeneic bone marrow transplant recipients, with 30% to 50% incidence of clinically significant

infection [25]. Common CMV-related complications include interstitial pneumonia, leukopenia, hepatitis, and gastroenteritis. CMV may also play a role in enhancing graft-versus-host disease in bone marrow transplant patients [1].

CMV disease is one of the most frequent opportunistic infections in patients with advanced HIV infection, of whom 40% develop sight-threatening or life-threatening disease [25]. CMV is considered a clinical marker for AIDS. The Centers for Disease Control and Prevention's surveillance case definition for AIDS includes CMV infection of the salivary glands that lasts longer than 1 month in adult patients [27]. CMV retinitis, one of the most common manifestations of the disease, is characterized by hemorrhagic retinal necrosis, spreading along retinal vessels and threatening sight when disease encroaches on the macula [28]. The widespread use of antiretroviral therapy has reduced the incidence of complications due to CMV infection; however, a newly recognized syndrome consequent to the use of highly active antiretroviral therapy has been described. Immune recovery vitritis has been reported in patients with inactive previously treated CMV retinitis because the CD4 cell count reconstitutes on antiretroviral therapy [29]. Although attributed to infiltrating T cells reacting to CMV antigens in the eye, the exact mechanism of immune recovery vitritis is not yet proven [25].

There are reports of CMV-related oral lesions in AIDS patients. They have been described as slowly enlarging ulcers [1]. One study reported that CMV was the sole ulcerogenic viral agent in a majority of oral lesions in a study population of AIDS patients [30]. Coinfection of oral ulcers with HSV and CMV has also been reported in AIDS patients [30,31]. Reports indicate that genomes of CMV are frequently detected in several different types of periodontal disease [32].

The diagnosis of CMV disease is made by histologic evaluation of suspected lesions, viral culture, antigen detection, and CMV DNA detection [27]. Biopsy specimens of CMV lesions demonstrate characteristic histopathologic changes, including enlarged cells with prominent intranucleolar and intracytoplasmic inclusions, referred to as "owl eye" cells [1]. Viral culture of suspected lesions is used to detect CMV; however, the major drawback is the prolonged length of time it takes for a positive culture to develop. Polymerase chain reaction techniques are becoming the standard assay for detecting CMV in most laboratories and can detect CMV in body fluids such as urine, blood, and saliva [1]. Salivary gland enlargement used to be a major clinical criterion for identifying CMV infection in infants due to the tendency of CMV to infect salivary glands [1].

Studies indicate that there is a relationship between xerostomia and the presence of CMV in saliva of HIV-infected individuals [33]. Prospective studies using viral culture, polymerase chain reaction techniques, and histopathologic examination demonstrated a significant correlation of xerostomia with presence of CMV in the saliva [34]. The results of this

study suggest a link between CMV in saliva and salivary gland dysfunction in HIV-infected patients.

Antiviral agents are used to treat CMV infections. Drugs such as ganciclovir, foscarnet, and cidofivir have been shown to be effective in treating CMV infections [25]. Newer drugs are currently in development for the treatment of CMV infections. Valganciclovir is a prodrug of ganciclovir that has greater oral absorption than ganciclovir [35]. Maribavir is a benzimidazole riboside derivative that is highly active against CMV in vitro [35]. Other drugs currently under development for use in treating CMV infections include tomeglovir, benzathiadazine-modified acyclonucleosides, and tricyclic inhibitors [35].

EBV

EBV is a herpesvirus that preferentially infects B lymphocytes. Infection of humans with EBV usually occurs by contact with oral secretions. The virus replicates in cells of the oropharynx and nearly all seropositive persons actively shed virus in the saliva [36]. Whereas most EBV infections of infants and children are asymptomatic or have nonspecific symptoms, infections of adolescents and adults frequently result in infectious mononucleosis [37,38]. Infectious mononucleosis from EBV has an incubation period of up to 8 weeks [1]. The initial symptoms consist of a triad of symptoms: fever, lymphadenopathy, and pharyngitis. Splenomegaly, hepatomegaly, oral ulcers, and palatal petechiae may also be present and the cervical lymph nodes are involved in greater than 90% of patients [1]. Less common complications include hemolytic anemia, thrombocytopenia, aplastic anemia, splenic rupture, and encephalitis [36]. The disease is usually self-limiting and most patients are well within 1 month.

Most patients with infectious mononucleosis have leukocytosis, with an absolute increase in the number of peripheral mononuclear cells, heterophile antibodies, elevated serum aminotransferase levels, and atypical lymphocytes [36]. Heterophile antibodies are immunoglobulins that clump sheep red blood cells and can be removed by absorption of beef red blood cells. The heterophile antibody test is positive in approximately 90% of cases [1]. Atypical lymphocytes are activated T lymphocytes that result from a normal lymphocyte response to EBV infection.

Chronic active EBV infection may be seen clinically. It is defined by a triad of clinical features: (1) severe illness of more than 6 months' duration that begins as a primary EBV infection or that is associated with abnormal EBV antibody titers, (2) histologic evidence of organ disease, and (3) demonstration of EBV antigens or EBV DNA in tissue [39].

There are various malignancies that are associated with EBV, including nasopharyngeal carcinoma, Burkitt's lymphoma, Hodgkin's disease, and lymphoproliferative disease. Nasopharyngeal carcinoma is prevalent in

southern China, northern Africa, and among Alaskan Eskimos. Nearly 100% of anaplastic or poorly differentiated nasopharyngeal carcinomas contain EBV genomes and express EBV proteins [36]. Burkitt's lymphoma is a high-grade malignant lymphoma of small, noncleaved B cells. In Africa, tumors of Burkitt's lymphoma usually present in the jaw, and over 90% of these cases are associated with EBV [36]. EBV DNA has been detected in tumors from 40% to 60% of patients with Hodgkin's disease in the United States [36]. EBV is associated with lymphoproliferative disease in patients with congenital or acquired immunodeficiency. Tissues from patients with EBV lymphoproliferative disease show plasmacytic hyperplasia, B-cell hyperplasia, B-cell lymphoma, or immunoblastic lymphoma [36].

Oral hairy leukoplakia is caused by EBV and occurs in a large percentage of HIV-infected patients and in some immunosuppressed transplant recipients [36]. It presents as a raised, white, corrugated lesion of the oral mucosa that commonly involves the lateral and/or ventral surfaces of the tongue. It may also appear as a plaquelike lesion and is often seen bilaterally. Multiple strains of EBV DNA may be present in the lesions.

HHV-6

HHV-6 was discovered in 1986 when it was isolated from peripheral blood lymphocytes of six individuals with lymphoproliferative disorders [40]. The virus was initially named human B-lymphotrophic virus because it was found within B lymphocytes of infected individuals. Later studies revealed that CD4 T cells were the major type of cell infected by HHV-6 [41,42]. Two variants of HHV-6 have been differentiated from one another: HHV-6A and HHV-6B.

Primary infection with HHV-6 can be asymptomatic, cause an unspecified febrile illness, or cause a specific clinical disorder: roseola (exanthema subitum) [43]. Most commonly, HHV-6 infects infants between the ages of 3 and 6 months. By the age of 3, 90% of the United States population has been infected with HHV-6 [43]. The virus is commonly isolated from saliva and respiratory transmission is the major route of primary infection.

HHV-6B is the particular subtype associated with roseola [44]. Children with roseola typically present with high fever without obvious signs of upper respiratory infection. The onset of a rash usually appears on the third day of fever, often coinciding with resolution of the fever. The rash of roseola is characterized by erythematous macules or slightly elevated papules on the head and neck [43].

Reactivation of HHV-6 has been reported in immunocompromised individuals and can lead to interstitial pneumonitis, bone marrow suppression, and widespread multi-organ infection [4,43]. HHV-6A is the subtype commonly reactivated in AIDS patients [42] and has also been

postulated as a cofactor in the progression of HIV disease [45]. Recently, there have been reports of severe drug-induced hypersensitivity syndromes associated with systemic HHV-6 reactivation [46,47].

Foscarnet, ganciclovir, and cidofivir have some antiviral activity against HHV-6 at high concentrations; however, they have limited practical use because of the need to administer them intravenously and the potential for severe side effects [43].

HHV-7

HHV-7 was discovered in 1990 when the virus was isolated from activated CD4 T cells obtained from a healthy individual. The genomes of HHV-7 and both variants of HHV-6 are closely related, with 20% to 75% nucleic acid homology, depending on the genes being compared [43].

Primary infection with HHV-7 is most often asymptomatic; however, it may cause a roseolalike illness. The peak age of initial infection is slightly later than that for HHV-6; the most common age range for infection is 18 months to 3 years of age [48]. By age 5 years, 90% of the United States population demonstrates evidence of HHV-7 infection [43]. HHV-7 is commonly isolated from saliva, and the mode of transmission is analogous to HHV-6 [4].

Similar to HHV-6, reactivation of HHV-7 in immunocompromised patients can lead to widespread multiorgan infection including encephalitis, pneumonitis, and hepatitis [43]. HHV-6 can be activated from latency by HHV-7 reactivation [49,50].

HHV-8

HHV-8 was isolated in tumor tissue from a patient with AIDS-associated KS in 1994 and named Kaposi's Sarcoma herpesvirus (KSHV) [51]. Moritz Kaposi, a Hungarian-born dermatologist, first described idiopathic multiple-pigmented sarcoma of the skin in 1872 and suggested a possible infectious etiology for KS [43].

Seropositivity rates for KSHV show strong racial and geographic variations. Infection rates are less than 3% in the United States and most European countries [51]. Infection rates are up to 25% in Mediterranean regions such as southern Italy and may be substantially more than 50% in Uganda and other Central African countries [52].

Primary or acute infection with KSHV in healthy individuals has been poorly defined. There have been isolated reports of transient fever, lymphadenopathy, and arthralgias coinciding with seroconversion of KSHV [53,54]; however, most primary KSHV infections appear to be asymptomatic. Most infected individuals, with normal immune systems, will not develop virus-associated disease.

KSHV has been localized to circulating B lymphocytes and, like EBV, B cells appear to be the major latent reservoir for KSHV in the blood [43].

Sexual transmission of KSHV is well established, particularly through male homosexual contact [51]. The prevalence of infection is associated with the number of homosexual partners and correlates with a history of sexually transmitted diseases [55]. KSHV has been detected within gastrointestinal mucosa of HIV-positive individuals, suggesting a possible basis for oral-fecal contamination [43]. KSHV has been readily detected in the saliva of most KS patients and in 15% to 33% of HIV-positive patients without KS, suggesting another mode of transmission [43]. Evidence supporting blood-borne transmission of KSHV is still relatively poor [56,57].

Like EBV, KSHV is capable of inducing malignant tumors in humans. Of the KSHV-associated malignant diseases, the most prominent is KS. The lesions of KS are multifocal and appear as reddish-purple macules or nodules. They are usually painless and appear on the lower extremities. HIV-associated KS can be more aggressive, and lesions may become more widespread and prominent, involving oropharyngeal and gastrointestinal mucous membranes [51]. Most intraoral KS lesions are found on the hard and soft palate, with a typical clinical appearance as previously described. Extrapalatal lesions may be seen on the gingiva and tongue; however, these are associated with a more rapid progression of KS and HIV disease [58]. Another malignant disease associated with KSHV is primary effusion lymphoma. Primary effusion lymphoma is found mainly in HIV-positive patients and presents as a lymphomatous growth in fluid that may affect the pleura, peritoneum, and pericardium [51]. In virtually all cases of primary effusion lymphoma, KSHV DNA is present. KSHV has also been linked to HIV-related cases of multicentric Castleman's disease, which is an aggressive disease that presents with multifocal lymphadenopathy and a variety of systemic symptoms such as fever, rash, and cytopenia [51]. The KSHV DNA sequences were found in all HIV-related cases of multicentric Castleman's disease [59], and the KSHV viral load in the peripheral blood tends to correlate with the severity of the disease [60]. Most recently, KSHV has been associated with another malignant process: anaplastic large-cell lymphoma [61].

Summary

Herpesviruses are responsible for many illnesses that affect the oral and maxillofacial region. The most common of these are primary or recurrent HSV infection, but knowledge of the manifestations of the eight herpesviruses that cause infections in humans will provide clinicians with a better understanding and basis for diagnosing and managing patients with these diseases. Immunocompromised patients are at greater risk for serious illness; therefore, clinicians treating transplant patients, patients receiving

cancer chemotherapy, or HIV-infected individuals should be aware of the various clinical manifestations of infection with herpesviruses.

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