Herpes Simplex Virus

1. INTRODUCTION

The herpesviruses (family Herpesviridae) are highly disseminated in nature. One of these ubiquitous pathogens, herpesvirus hominis, is the etiologic agent of herpes simplex in humans. Forty years after the isolation of the herpes simplex viruses (HSV), Schneweiss (1) established the existence of two serotypes, HSV-1 and HSV-2, currently designated under The International Committee on Taxonomy of Viruses (ICTV) rules as human herpes viruses 1 and 2 (2). Type 1 infections are primarily nongenital (e.g., herpes labialis and ocular herpes), whereas type 2 infections are primarily genital (herpes genitales).

Since their discovery, nearly 100 herpesviruses have been, at least partially characterized, and six of them have been isolated from humans: HSV-1 (3–8), HSV-2 (3–10), human cytomegalovirus (HCMV) (11), varicella-zoster virus (VZV) (12–14), Epstein-Barr virus (EBV) (15,16), and human herpesvirus 6 (HHV6) (17,18). Diagnosis of HSV infections may be difficult because of the ability of these viruses to establish latency and often to shed intermittently in the absence of invasive disease (19).

Compared to immunocompetent patients, HSV infections in immunocompromised hosts caused a more severe and invasive illness characterized by prolonged viral shedding and a tendency to heal more slowly. This, coupled with the emergence of resistant strains (isolated exclusively from immunocompromised patients) and frequent reactivation (20) requires a more aggressive and targeted antiviral therapy (21).

Prior to the emergence of the AIDS pandemic, chronic mucocutaneous HSV infections have been primarily seen in patients with congenital cellular immune deficiencies, or acquired immune defects associated most often with lymphoproliferative malignancies (22–24) and organ transplantations (22,24–29). Thus, 80% of marrow transplant recipients with antibody to HSV before transplantation have reactivated virus after the transplantation (27,30,31). The absence of specific cellular immune response to HSV during the first month after the transplant significantly contributes to the severe, prolonged, and debilitating course of HSV disease (30). Frequent reactivation has been also reported in renal-transplant recipients (32,33) and in patients receiving leukemic induction therapy (34).

Currently, HIV-infected patients represent the major population affected by persistent active HSV infections (35). The significant association of HSV-induced genital ulceration and transmission of HIV has been shown in many studies (36). Furthermore, because asymptomatic shedding of HSV can continue despite clinically effective suppression with antiviral chemotherapy, the possibility of person-to-person transmission persists (37).

Mucocutaneous HSV infections in immunocompromised patients may be much more severe than in normal subjects. The lesions tend to be more invasive, slower to heal, and associated with prolonged viral shedding (38).
Because seropositivity for HSV is high in HIV-positive patients, it is very likely that clinical HSV disease is associated with reactivation of latent virus (39). The most common clinical manifestations, usually identified with a high morbidity and mortality rate include orolabial, genital, and anorectal mucocutaneous lesions; esophagitis (40); and less often encephalitis. According to the Centers for Disease Control (CDC) definition (41), ulcerative HSV lesions that have been present for more than 1 mo in an HIV-positive individual, or in persons with no other apparent cause of immunodeficiency, are considered an AIDS-defining condition. However, herpetic esophagitis, although frequent infection in immunocompromised patients, has also been diagnosed in immunocompetent hosts (42).

Chronic perianal HSV lesions causing severe morbidity (pain, itching, and painful defecation), have been considered among the first opportunistic infections associated with AIDS in homosexual men (43). Although HSV perianal infections are common in immunocompromised patients, the cutaneous presentation in these patients may be often atypical (large, chronic, hyperkeratotic ulcers [44]) and overlapping with the clinical features of other diseases, thereby posing difficulty in diagnosis (45). The clinical manifestations of orolabial and genital HSV disease in HIV-infected patients (mild to severe tissue-distructive lesions) are usually similar to that observed in other immunosuppressed individuals (39).

HSV-induced encephalitis (46,47) (a focal or global inflammation of the brain caused by invasion of the brain parenchyma by viruses, bacteria, parasites, or fungi) is a life-threatening condition with substantial morbidity and mortality despite the use of antiviral therapy (48,49). Cases of HSV encephalitis in AIDS patients usually occur as complications of orolabial HSV infection. Another orolabial HSV-induced complication is a reported case of inferior alveolar nerve infection (50).

Herpetic geometric glossitis, a recently described form of lingual HSV-1 infection, has been reported in several HIV-positive patients, as well as one cardiac and one pediatric patient with acute myelogenous leukemia (AML) (31,51). Results from a report by Woo and Lee (52) demonstrated that oral recrudescent HSV infections may involve any intraoral site in immunocompromised patients with nonkeratinized sites representing nearly half of all cases. Hence, it is advisable that all oral ulcers in immunocompromised patients should be cultured for HSV regardless of their location.

Although HSV disease affects primarily the upper respiratory tract (53,54), lower respiratory tract infections have also been reported (55). In a study by Ramsey et al. (56), mucocutaneous lesions antedated the pneumonia in 17 of 21 patients with HSV pneumonitis. HSV-associated pneumonitis has been diagnosed in immunocompromised patients (57–60), alcoholic hepatitis (61), burn victims (62,63), trauma patients (64), and as a consequence of disseminated HSV infection in neonates (65,66). Although the majority of cases affected adults, HSV pneumonitis has also been described in children (55–58,62,63,67–69). A rare case of disseminated neonatal HSV infection has been reported (70).

Hepatitis is an unusual and often fatal manifestation of HSV infection (71,72). Impaired immunity resulting from pregnancy, malignancy, immunosuppression, or inhalational anesthetics may be predisposing factors. Another unusual site involved is colonic HSV disease (73).

An interesting case of latanoprost-associated recurrent HSV keratitis was reported by Dios Castro and Maquet Dusart (74). The patient (with a past episode of herpetic keratitis 21 yr previously), developed the HSV infection after starting treatment with latanoprost.

2. TREATMENT OF HERPES SIMPLEX VIRUS INFECTIONS

In both immunocompromised and immunocompetent patients, acyclovir demonstrated a high degree of clinical efficacy and no statistically significant differences between acyclovir and placebo for mild or major adverse effects. The availability of acyclovir as a generic preparation will further improve the benefit-to-cost ratio. However, the emergence of HSV resistance to antiviral drugs is of concern, and establishing alternative treatments is very important. Newer drugs (valaciclovir, famciclovir, penciclovir) with high oral bioavailability have the added benefit of less frequent administration and avoidance of intravenous therapy in many cases (75–78).