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Genital Zoster Infection: the Great Imposter

Paul A. Granato, Ph.D., DABMM, FAAM, Microbiology Department, Laboratory Alliance of Central New York and Department of Pathology, SUNY Upstate Medical University, Syracuse, New York

Abstract

Herpes simplex virus 1 (HSV-1), herpes simplex virus 2 (HSV-2), and varicella-zoster virus (VZV) are taxonomically closely related viruses that produce clinically distinct diseases but share common features of infection. HSV-1 and HSV-2 both produce cutaneous and mucocutaneous primary infections followed by reactivation disease occurring at the same or a nearby anatomic site. Primary VZV infection, also known as chickenpox, is usually a childhood disease that produces pox-like cutaneous lesions distributed over the entire body. Reactivation VZV infection, often called herpes zoster, generally occurs later in life but, unlike HSV disease, produces pox-like lesions at a different anatomic location, typically along dermatomes. As such, the clinical differential diagnosis of reactivation HSV infection and zoster is generally based upon the anatomic location and the appearance of the lesion(s). The recent availability of molecular assays has resulted in the unexpected diagnosis of zoster infections in male and female patients who presented with genital lesions. The purpose of this article is to present a brief overview of HSV and VZV infections and to relate a laboratory experience that resulted in the diagnosis of zoster infections using a molecular assay in which almost 10% of the 282 positive VZV specimens were from genital sites.

Introduction

There are at least eight known herpesviruses classified within the family *Herpesviridae* that are divided into three major groups based upon their genomic and biologic characteristics: the alphaherpesviruses (herpes simplex virus 1 [HSV-1], herpes simplex virus 2 [HSV-2], and varicella-zoster virus [VZV]), the betaherpesviruses (cytomegalovirus, human herpes virus 6, and human herpes virus 7), and the gammaherpesviruses (Epstein-Barr virus and Kaposi's sarcoma-associated herpesvirus, also known as human herpesvirus 8). All of these viruses are morphologically similar and possess a double-stranded DNA and a lipid envelope [1,2]. Despite such similarities, these viruses produce markedly different diseases, and HSV-1, HSV-2, and VZV are the focus of this article.

HSV and VZV Infections: Similarities and Differences

HSV and VZV produce clinically distinct diseases but share common features of infection [3]. Primary HSV and VZV infections produce characteristic but different lesions on skin and mucous membranes. For both viruses, once the primary stage of infection has resolved, HSV and VZV travel along and reside in the neuronal nuclei of the sensory ganglia, where they remain dormant in a latent state. These viruses may remain dormant throughout an individual's life or cause reactivation disease.

Reactivation HSV infection produces cutaneous and mucocutaneous lesions similar in appearance to those of the primary infection and at the same or a nearby anatomic location, while reactivation VZV infection produces a markedly different clinical presentation than primary chickenpox infection, with the lesions developing in a different anatomic location, usually, but not always, along dermatomes.

HSV Infections

HSV-1 and HSV-2 can cause a variety of localized infections, depending on the mode of

Corresponding author: Paul A. Granato, Ph.D., Director of Microbiology/ Scientific Director, Laboratory Alliance of Central New York, 113 Innovation Lane, Liverpool, NY 13088. Tel.: 315-410-7036. E-mail: granatop@upstate.edu.

transmission and a few more serious, life-threatening, systemic infections, such as herpes encephalitis and herpes meningoencephalitis. Localized infections are typically acquired by direct contact with an asymptomatic infected individual or by contact with an active lesion. These localized infections, among which herpes labialis (cold sores) and herpes genitalis (genital herpes) are the most common, may involve a variety of different anatomic sites. The CDC estimates that 776,000 people in the United States acquire new genital herpes infections each year [4].

Stages of HSV Infection

Cutaneous and mucocutaneous primary HSV infections produce three different characteristic lesions during the symptomatic stages of the disease process: the vesicular lesion, the ulcerative lesion, and the crusted lesion. The most common anatomic location of primary infection is usually on an oral or genital cutaneous/mucocutaneous site, depending on the mode of direct contact. It is mistakenly thought that HSV-1 causes infections above the waist while HSV-2 causes infections below the waist. However, HSV-1 and HSV-2 are not restricted by anatomic boundaries, and each virus can cause infection at either anatomic site, depending on the mode of transmission.

Localized HSV infections involve two stages: the lytic stage and the latent stage [5]. The lytic stage represents the symptomatic period of infection, while the latent stage is characterized by dormancy when the disease is in remission.

The lytic stage of HSV infection is diagrammatically presented in Fig. 1, which shows the time line for the various stages of lesion development during the cycle of symptomatic infection. Following exposure to HSV and an incubation period of several days, HSV infects epithelial cells, resulting in cellular destruction, and elicits a host response to produce a vesicular or blister-like lesion(s). The vesicle grows in size over several days, causing its rupture to produce a painful, wet, ulcerative lesion. After 5 to 7 days, the ulcerative lesion resolves to produce a dry, crusted lesion (Fig. 2) that eventually heals and disappears.

The lesions characteristic of primary infection (vesicular, ulcerative, and crusted) typically occur over a 3-week interval. Importantly, as shown in Fig. 1, the vesicular and ulcerative stages of the disease are highly contagious following direct contact due to the shedding of large quantities of viral particles [1,6].

The latent cycle of HSV infection begins during the symptomatic stage of infection, in which the virus, or more likely its nucleocapsid, is transported intra-axonally to neuronal cell bodies to establish latent infection [7]. For oral HSV disease, the trigeminal ganglia are most commonly affected, but involvement of superior and inferior cervical ganglia may also occur [8,9]. With HSV genital infections, the sacral root ganglia (S2 to S5) are most commonly affected in the latent stage [10].

HSV-1 and HSV-2 infections are life-long, and reactivation disease usually occurs at or near the anatomic site of primary infection. Activation of latent infection can be triggered by a number of factors, including the immunologic status of the host, high altitude,

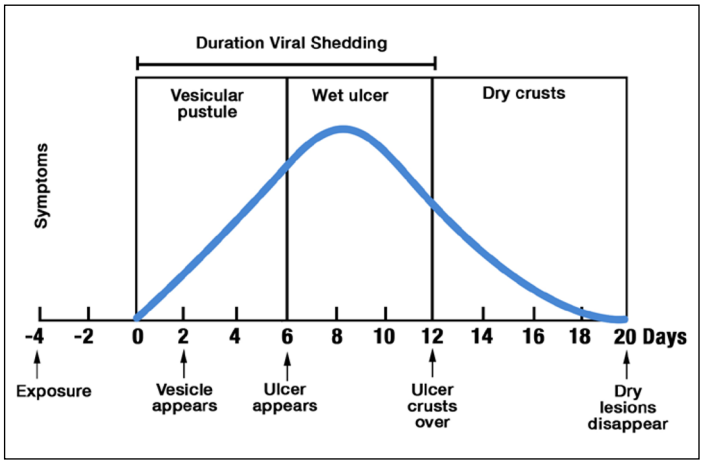

Figure 1. Lytic stage of HSV infection. The diagram illustrates the timeline and three stages of lesion development during the cycle of symptomatic infection, or lytic stage.

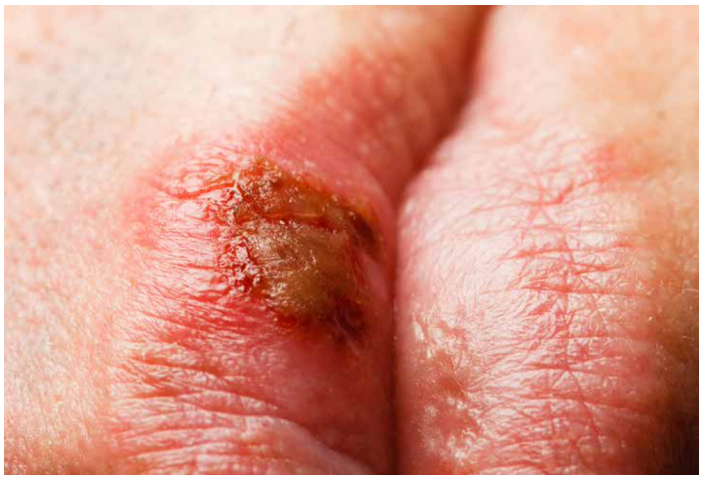

Figure 2. A crusted oral lesion of HSV.
Source: iStock; scottjay, photographer

ultraviolet sunlight exposure, fever, and possibly stress [6]. When reactivation disease occurs, the viral nucleocapsid travels down the axon to the anatomic site of primary infection to repeat the cycle of symptomatic lytic infection. The cycle of symptomatic reactivation disease followed by dormancy can continue throughout an individual's life. Typically, recurrent infections are less pronounced than primary infections and resolve more rapidly [11,12].

VZV Clinical Infections

VZV is the cause of two distinct clinical diseases: chickenpox and herpes zoster, also known simply as zoster or shingles. Chickenpox, or varicella, is the primary infection of VZV and results from exposure of an immunologically susceptible host to an infected individual. Disease transmission is usually by the respiratory route following inhalation of infectious aerosols, but disease may also be acquired by coming into direct contact with an active lesion.

After an incubation period of 10 to 21 days following exposure to an infected individual, the clinical appearance of chickenpox becomes manifest by the development of a generalized vesicular