PRIMARY HERPETIC GINGIVOSTOMATITIS: A CASE REPORT AND REVIEW OF LITERATURE

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Abstract

Acute Herpetic Gingivostomatitis represents the main pattern of primary infection with herpes simplex viruses. HSV is a double-stranded DNA virus and is a member of the human herpes virus (HHV) family officially known as *Herpetoviridae*. More than 90% of Acute Herpetic Gingivostomatitis cases are caused by the herpes simplex virus type I (HSV-I) and occasionally by herpes simplex virus type II (HSV-II). The infection is acquired by close oral mucosa contact with infected saliva or perioral lesions. Acute herpetic gingivostomatitis mostly occurs during childhood or teenage years. The infection is largely asymptomatic, with clear clinical manifestations in only 10% of patients. Here we report a case of 24 year old male patient with Acute Herpetic Gingivostomatitis with classic clinical manifestations.

Key Words: Herpes Simplex, Infections, Oral lesions

Introduction

Herpes simplex, an acute infectious disease is the most common viral disease affecting man. The tissue preferentially involved by herpes simplex virus now often referred to as herpes hominis are derived from ectoderm and consist principally of skin, mucous membrane, eyes and central nervous system.[1] There are 80 known herpes viruses, and eight of them are known to cause infection in humans: herpes simplex virus (HSV) 1 and 2, varicella-zoster virus, *Cytomegalovirus*, Epstein-Barr virus, and human herpes virus 6 (HHV6). All herpes viruses contain a deoxyribonucleic acid (DNA) nucleus and can remain latent in host neural cells, thereby evading the host immune response. In immunocompromised patients, HHV6 can cause interstitial pneumonitis and bone marrow suppression and HHV8 has been closely associated with Kaposi's sarcoma.[2] There are 2 immunologically different types of HSV: Type 1 – usually affecting the face, lips, oral cavity and upper body skin and Type 2 – usually affecting the genitals and skin of lower body.[1]

CASE REPORT

A 24 year male patient reported to the department of oral medicine and radiology with chief complain of ulcer on lower lip associated with pain since 3 days. He also gave history of fever prior to the ulcerations. Medical history and family history were non-contributory and on general physical examination all the vital signs were within normal limits. (Figure 1)

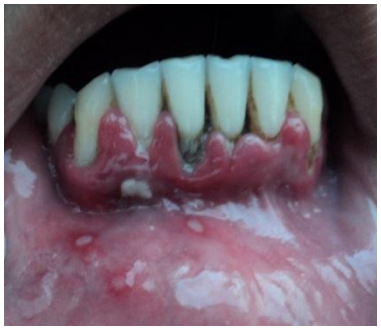

Figure 1: Multiple shallow ulcers in relation to lower labial mucosa

On extra oral examination submandibular lymph nodes were palpable both on left and right side which were mobile, tender and soft in consistency and on intra oral examination multiple shallow ulcers measuring less than 0.5cm were seen on lower labial mucosa surrounded by a erythematous area.

Linear marginal erythema in relation to upper right quadrant was present (Figure 2).

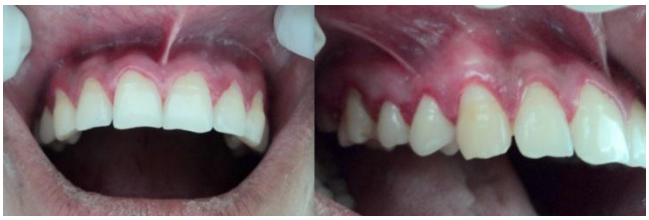

Figure 2: Linear marginal Erythema

Based on history and clinical findings a provisional diagnosis of acute herpetic gingivostomatitis was given with differential diagnosis of herpetiform apthous stomatitis, acute necrotising ulcerative gingivitis, allergic stomatitis, erythema multiforme and ulcers due to chemotherapy. Routine haemogram revealed all the values within the normal limits except for ESR which was raised. Patient was advised topical application of antiseptic and anaesthetic 3-4 times daily and paracetemol was prescribed for 5 days along with multivitamins. The lesion subsided after a weeks' time (Figure 3).

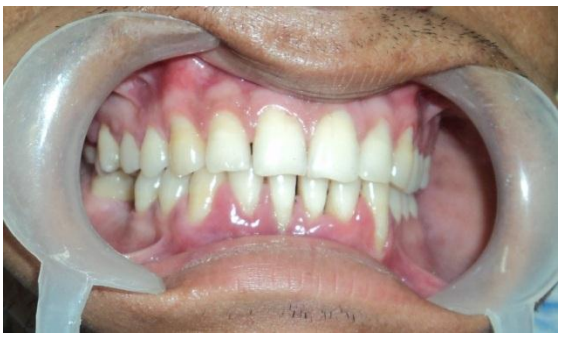

Figure 3: Post treatment – after one week

Discussion

HSV1, HSV2, and varicella-zoster are viruses that are known to cause oral mucosal disease.[1] The herpes simplex virus is composed of four layers: an inner core of linear double-stranded DNA, a protein capsid, a tegument, and a lipid envelope containing glycoproteins that is derived from the nuclear membrane of host cells. The two major types, HSV 1 and 2, can be distinguished serologically or by restriction endonuclease analysis of the nuclear DNA. Classically, HSV1 causes a majority of cases of oral and pharyngeal infection, meningoencephalitis, and dermatitis above the waist; HSV2 is implicated in most genital infections. Although this distinction applies to a majority of cases, changing sexual habits are making that distinction less important. Both types can cause primary or recurrent infection of either the oral or the genital area, and both may cause recurrent disease at either site. Humans are the only natural reservoir of HSV infection, and spread occurs by direct intimate contact with lesions or secretions from an asymptomatic carrier. Latency, a characteristic of all herpes viruses, occurs when the virus is transported from mucosal or cutaneous nerve endings by neurons to ganglia where the HSV viral genome remains present in a non-replicating state. During the latent phase, herpes DNA is detectable, but viral proteins are not produced. Reactivation of the latent virus occurs when HSV switches to a replicative state; this can occur as a result of a number of factors including peripheral tissue injury from trauma or sunburn, fever, or immunosuppression.[2]

Etiopathogenesis

Herpes simplex viruses type 1 (HSV-1) and HSV-2 are responsible for primary and recurrent mucocutaneous herpetic infections. Most herpetic infections are transmitted from infected persons to others through direct contact with a lesion or infected body fluids, e.g., vesicular exudates, saliva, and genital fluids. Following exposure, the virions attach to host Cells mediated by envelop-related viral proteins that bind specific receptors on host-cell membrane. Once the virus has gained entry into the cytoplasm, it loses its capsid proteins by the process known as un-coating and the viral nucleic acid is transported into the host-cell nucleus. In the host-cell nucleus, the viral genome is replicated. Replication requires the generation of protein kinase-dependent nucleoside triphosphates, which are incorporated into the new viral genome by viral polymerases. In the next step, the new viral genome is transcribed into mRNA, which subsequently is translocated to host-cell ribosomes. The viral proteins synthesized by host-cell ribosomes are assembled with the duplicate viral genome. Assembly is followed by maturation, a process essential for the newly formed virions to become infectious. The late cytopathogenic effect of HSV-1 and HSV-2 infections is characterized by general disintegration of host epithelial cells and the egress of infectious viral units into the extracellular environment. The newly synthesized viruses, in turn, may infect other epithelial cells or enter sensory nerve endings.[3] (Figure 4)

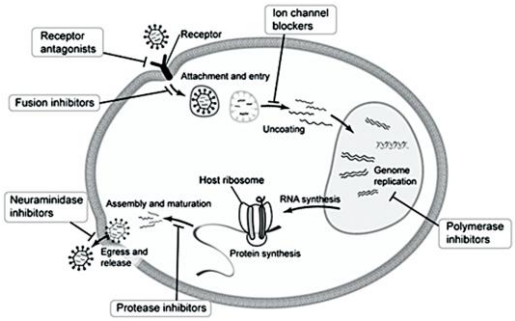

Figure 4: - Stages of the viral life cycle and potential targets for antiviral agents

Following primary infection at mucocutaneous sites, both HSV-1 and HSV-2 enter sensory nerve endings and are transported via retrograde axonal transport to regional sensory ganglia where they establish latency in neuronal cell bodies. The most frequent site of latency for HSV-1 is the trigeminal ganglion and for HSV-2 it is the lumbosacral ganglia.[4] Within neurons, the virus exists in an immunologically shielded state until reactivation is triggered spontaneously or by a number of different stimuli, e.g., exposure to ultraviolet light, mechanical trauma, fever, dietary factors, and immunosuppression.(Figure 5)

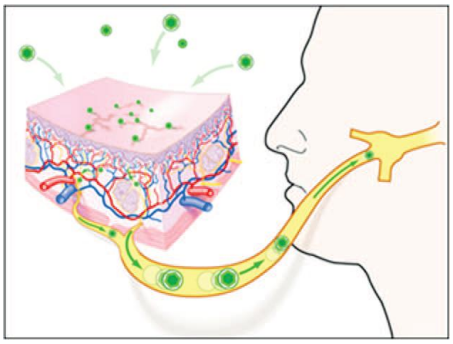

Figure 5: - Retrograde axoplasmic transport of the HSV following reactivation

When the HSV is reactivated, newly produced virions spread from infected neurons by anterograde axoplasmic transport to mucocutaneous sites causing recurrent herpetic infection.[3] (Figure 6)

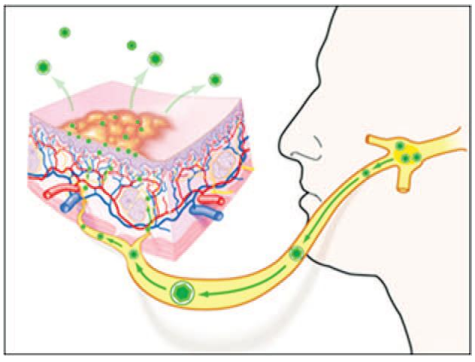

Figure 6: - Anterograde axoplasmic transport of the HSV following primary infection

The ability of the HSV to establish latency in a host provides for a huge viral reservoir. While in the past, infectivity was believed to be closely tied to clinical evidence of infection; viral reactivation, just like primary infections, does not always result in clinical disease. It has been documented that at least 70% of the population shed HSV-1 asymptomatically at least once a month and many individuals appear to shed the virus more than 6 times a month, contributing to the dissemination of HSV-1.[5] The mean duration of viral shedding was reported to be between 1 and 3 days, but viral shedding for periods longer than 3 days was observed in about 10% of the patients. Asymptomatic viral shedding is also advanced as a surrogate marker for the transmission of genital herpes.[6]

Clinical manifestations

Primary herpetic gingivostomatitis (PHG) represents the main pattern of primary infection with herpes simplex viruses.[7] More than 90% of PHG cases are caused by the herpes simplex virus type I (HSV-I) and occasionally by herpes simplex virus type II (HSV-II).[8-9] The overwhelming majority of primary infections is asymptomatic or is so mild that it goes unnoticed. In symptomatic patients, following an incubation period of 2-20 days, prodromal non-pathognomonic signs and symptoms include fever, chills, malaise, irritability, headache, and anorexia. The onset of the acute phase is abrupt and is usually characterized by pain, salivation, fetor oris, and sub-mandibular and cervical lymphadenopathy. Examination reveals inflammation of the marginal and attached gingivae characterized by erythema, edema, capillary proliferation and widespread vesicular eruptions affecting vermilion border of lip and labial mucosa, tongue, buccal and vestibular mucosa, hard and soft palate,floor of the mouth, tonsillar and pharyngealmucosa. New vesicles continue to erupt for3 to 5 days, coalesce, rupture within 24 to 48hours, and produce shallow, painful, irregular erosions or ulcers circumscribed by a red halo. Gradual healing, without scaring occurs within 7 to 14 days however HSV may continue to be present in the saliva for up to a month after the onset of disease. PHGS in immunocompromised patients tends to be more severe, last longer, and may lead to systemic viremia.[2-3] Other symptoms common in primary herpes are halitosis, excessive drooling, and hypersalivation.[10] Dehydration is a common complication of primary herpes resulting from discomfort in eating and drinking.[11] Other complications include Bell's palsy, viremia, ocular involvement, herpetic esophagitis, and meningoencephalitis.[12-13]

Differential diagnosis

The primary herpetic gingivostomatitis presents with multiple ulceration in oral cavity involving the labial mucosa, buccal mucosa, floor of the mouth which are pin point shallow ulcers present on erythematous base coalesce to form large irregular ulcers with the tissue tags. It has to be differentiated clinically from herpetiform apthous stomatitis, recurrent HSV infection, acute necrotising ulcerative gingivitis, allergic stomatitis, erythema multiforme and ulcers due to chemotherapy. Whereas the recurrent herpetic infection occurs usually at the Vermilion border of the lip recurring periodically, however intraoral lesions are seen on the gingiva, palate and alveolar mucosa usually associated with prodromal symptoms of tingling and burning sensation. Apthous ulcers are round symmetrical and shallow surrounded by erythmatous halo, present on labile mucosa, often associated with prodromal symptoms. erythema multiforme lesions are large, irregular, deeper and often bleed, within 2-3 days the lesion begin to crust and gingival involvement is rare and presence of target lesions on the skin are pathognomonic.[1-2] In case of ANUG the ulcers are necrotic and punched out seen on interdental papilla and marginal gingiva which are associated with pain, tenderness, profuse salivation, a peculiar metallic taste. Teeth are sensitive to pressure or have a woody sensation.[2] Allergic stomatitis results from contact with dental materials, oral hygiene products or foods. The reaction only occurs at site of contact and includes burning sensation or soreness accompanied by erythema and occasionally formations of vesicles and ulcers and is most accurately diagnosed by patch test.[2] Ulcer due to chemotherapy and recurrent HSV infection can be ruled out by taking appropriate history from the patient.

Laboratory Diagnosis

The diagnosis of primary herpetic gingivostomatitis is straight forward when patients present with a typical clinical picture of generalized symptoms followed by an eruption of oral vesicles, round shallow symmetric oral ulcers, and acute marginal gingivitis. Laboratory tests are rarely required in these cases. Other patients, especially adults, may have a less typical clinical picture, making the diagnosis more difficult.[2]

Direct smears

A Wright-Giemsa-stained preparation (Tzanck smear) of a herpetic skin vesicle may contain intranuclear inclusions and fused multi-nucleated squamous epithelial cells, lipzuts bodies; however, these diagnostic findings are seen only in 50 to 67% of vesicular lesions As herpetic lesions ulcerate, smear sensitivity dramatically decreases.[14]

Cell culture

Viral culture has been long-recognized as the "gold standard" method for the laboratory diagnosis of HSV infection. A variety of human and nonhuman primary embryonic cells, human diploid cell lines, and continuous human or primate cell lines have been successfully employed in traditional tube cultures.[15-16] Other than the choice of cells, many factors influence the sensitivity and time to culture positivity (as judged by observation of typical cytopathic effect) including quality, age, and passage number of cells; cell pre-treatment and adsorption conditions: incubation temperature and conditions (stationary vs. roller cultures); and composition of culture medium.[17] Because HSV can usually be recovered by culture in a relatively short time, serologic diagnosis of infection is not generally employed when cultures of

lesions can be easily obtained. HSV-specific IgG can be detected readily using a number of commercially available indirect immunofluorescence tests or enzyme immunoassays. Antibody titres of acute sera and convalescent sera can differentiate between primary and secondary HSV infection. If antibody titre is increased in convalescent sera as compared to acute sera, then it is considered as primary HSV and if the acute sera and the convalescent sera are same then it is considered as secondary HSV.

Nucleic acid amplification assays

Culture is clearly more sensitive than direct smear tests, but nucleic acid amplification assays add 10 to 30% more positive results than culture. Although several amplification technologies are available, PCR is currently the most commonly used method for the sensitive detection of HSV[18-19]. PCR identification of HSV DNA in spinal fluid is now the test of choice for herpetic encephalitis. PCR can also identify HSV in any type of specimen (swabs of mucocutaneous lesions, ocular fluid, bronchial wash, tissue biopsies, etc.); HSV DNA is stable in samples held at 4°C, and can identify as few as 0.2 to 0.5 HSV copies per microliter of spinal fluid or viral transport medium. PCR is eight times more sensitive than culture for identification of asymptomatic mucocutaneous viral shedding. The specificity of PCR identification of HSV is virtually 100%, and real-time PCR methods can also reliably differentiate HSV-1 from HSV-2.[14]

Management

Palliative and supportive management of orolabial herpetic infections variably consists of controlling fever and pain, preventing dehydration, and shortening the duration of lesions. Antiviral chemotherapy is available for the treatment of patients at increased risk of complications.[3] Primary line of treatment includes dietary supplements, and patients should be advised to rest, avoid smoking tobacco products and drinking alcoholic beverages, eat a soft balanced diet, and ensure an adequate intake of fluids, vitamins, and minerals.[2-3] Topical anesthetics, analgesics, and antipyretics, Rinsing with lidocaine viscous 2% before each meal, effectively reduces pain during eating. The agent spreads easily because of its high viscosity and low surface tension, and it adheres well to tissues. Care should be taken to prevent possible aspiration of food because the agent may interfere with the pharyngeal phase of swallowing. In addition, topical lidocaine in pediatric patients has been associated with an increased risk of seizure. Benzocaine, 20%, may be a better alternative in the management of the young and the debilitated when aspiration and the possibility of excessive systemic absorption are a concern. Benzocaine has a rapid onset and short duration of action, but virtually no systemic absorption occurs through the mucous membranes. Elixir of diphenhydramine hydrochloride, 12.5 mg/5 ml, in combination with Maalox, is another option, especially in children. Side effects and adverse reactions are not expected when the drug is used topically. Because PHGS is associated with constitutional symptoms, the administration of acetaminophen may be indicated. Acetaminophen, an analgesic/antipyretic agent, provides adequate patient comfort.[3]

Acyclovir

In cases of severe PHGS and in the management of immunocompromised patients (e.g., patients with AIDS, organ transplant recipients, and patients on chemotherapy) oral or parenteral acyclovir should be added to the primary line of treatment.[20] Systemic acyclovir accelerates the resolution of viral shedding and healing time, and reduces pain. Acyclovir is generally well tolerated however, Common adverse effects include nausea, vomiting, and headache and, rarely, oral acyclovir have been associated with tremors, hallucinations, seizures, and coma. Intravenous infusion increases the risk of reversible renal toxicity.[3] Patients with severe PHGS and immunocompromised patients who cannot tolerate acyclovir or who fail to respond to acyclovir may respond to foscarnet.[20] Topical application of acyclovir is also available for application on the lesion .

Natural Remedies for *Herpes simplex*

Dietary Factors

Ingestion of large amounts of refined carbohydrates impairs certain parameters of immune function. Although the relationship between refined-carbohydrate intake and susceptibility to *Herpes simplex* has not been investigated, many patients have observed that herpetic lesions recur when they eat too many sweets. In some cases, ingestion of even small amounts of refined sugar appears to trigger an exacerbation.[21]

Lysine/Arginine

The proteins synthesized by HSV contain more arginine and less lysine than proteins synthesized by host cells arginine is required for HSV replication and Lysine appears to antagonize arginine by several mechanisms.[22] Forty-five patients with frequently recurring *Herpes simplex* infections received lysine (usually 312-1,200 mg per day) for periods of two months to three years. Foods high in arginine were restricted. Lysine treatment appeared to reduce the frequency of recurrences. When lysine was discontinued, lesions usually recurred within 1-4 weeks.[23]

Vitamin C

Ascorbic acid has been shown to inactivate a wide range of viruses *in vitro*, including *Herpes simplex* virus[24], and to enhance immune function. As early as 1936, vitamin C was reported to be of value in the treatment of *Herpes simplex*. Klenner stated in 1949 that administering massive parenteral doses of vitamin C accelerated the healing of herpes lesions.[25] Cathcart later noted that herpes lesions in AIDS patients responded to a combination of oral and intravenous vitamin C and frequent topical application of vitamin C paste (ascorbic acid or sodium ascorbate mixed with water). For treatment of an acute episode, up to 10,000

mg per day or more, according to bowel tolerance, for 5-10 days might be considered.[21]

Zinc

Zinc ions have been shown to inhibit the replication of HSV-1 and -2 *in vitro*. At a concentration of 0.1 mM, the inhibition was almost complete and appeared to result from selective inhibition of the viral DNA polymerase. It was suggested that this treatment be considered for prophylaxis prior to sun exposure for patients who experience sun-induced herpetic outbreaks.[24]

Vitamin E

In uncontrolled trials, topical application of vitamin E relieved pain and aided in the healing of oral herpetic lesions (gingivostomatitis or herpetic cold sores). In two studies, the affected area was dried and cotton saturated with vitamin E oil (20,000-28,000 IU per ounce) was placed over it for 15 minutes. [25-26] Pain relief occurred within 15 minutes to eight hours, and the lesions regressed more rapidly than usual. In another study of 50 patients with herpetic cold sores, the content of a vitamin E capsule was applied to the lesions every four hours. Prompt and sustained pain relief occurred and the lesions healed more rapidly than expected.[27]

Lithium

Preliminary evidence suggests that oral or topical lithium is beneficial. Lithium inhibited the
Replication of HSV-1 and HSV-2 *in vitro* at concentrations that did not inhibit host cell replication.[28]

Conclusion

Acute herpetic gingivostomatitis is more often observed in young adults than in children. Most of the cases present with widespread oral lesions. Though Orolabial herpetic infections are usually self-limiting successful management of such cases is necessary. Their treatment is primarily palliative and supportive directed toward controlling the signs and symptoms of the particular condition under consideration. Antiviral chemotherapy is given to patients with exacerbated manifestations and immunocompromised patients. Herpetic infections should also be considered as an occupational hazard in oral healthcare settings therefore carefully recorded & managed.

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