Oral viral infections and the therapeutic use of antiviral agents in dentistry

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Abstract
This paper reviews the current concepts of viral classification, infection and replication. The clinical presentation of common oral viral infections encountered in the dental practice are discussed, including: herpes simplex virus types 1 and 2; Epstein-Barr virus; varicella-zoster virus; Coxsackie virus; human papilloma virus; and human immunodeficiency virus. The diagnosis, principles of management and pharmacological agents available for the treatment of oral viral infections are also discussed.

Key words: Virology, antiviral agents, dentistry.

Abbreviations and acronyms: AIDS = acquired immune deficiency virus; dsDNA = double-stranded DNA; dsRNA = double-stranded RNA; EBV = Epstein-Barr virus; FEH = focal epithelial hyperplasia; HIV = human immunodeficiency virus; HPV = human papilloma virus; HSV-1 = herpes simplex virus type 1; HSV-2 = herpes simplex virus type 2; KS = Kaposi’s sarcoma; OHL = oral hairy leukoplakia; SCP = squamous cell papilloma; ssDNA = single-stranded DNA; ssRNA = single-stranded RNA.

Virology
Classification of viruses
Viruses are not self-reproducing. They need the presence of another organism or host to reproduce or replicate. The host possesses ribosomes which the virus itself cannot synthesize. Viruses contain only one type of nucleic acid, either DNA or RNA. They are reproduced solely from their nucleic acid, i.e., a virus never arises directly from a pre-existing virus.

Nearly all human viruses are icosahedral and possess a protein shell (nucleocapsid). Some also have an envelope surrounding the capsid. This envelope is made from lipids which are derived from host cell membranes. Protein ‘spikes’ project from the surface of viral nucleocapsids. The proteins are normally glycoproteins which serve the virus in attachment and infection of the host. The area inside the nucleocapsid is referred to as the core.

Four different types of nucleic acid genomes are found in human viruses: single-stranded DNA (ssDNA), double-stranded DNA (dsDNA), single-stranded RNA (ssRNA) and double-stranded RNA (dsRNA).

Viral infection and replication
The outcome of viral infection is dependant upon the viral state. If the virus is in a lytic state, the host cell is destroyed, releasing progeny virus into the surrounding medium. In lysogeny, the virus integrates its genome into the host genome. At a later date, the viral genome may be activated and can enter a lytic state. In latency, a form of lysogeny, the viral genome stays in the host cell, but is not necessarily incorporated. The genome is present but does not produce many products. Again, the viral genome can be reactivated, generating disease in the host. The process of viral infection has two stages: attachment and penetration. Viruses attach to their host cells by way of cellular receptors. A cell cannot be infected unless it expresses the molecule which serves as a receptor for that particular virus on its outer surface. Enveloped viruses can penetrate cells by fusing with the host cell membrane, while both enveloped and naked viruses can penetrate by receptor-mediated endocytosis. Once the viral genome is released, early gene transcription begins. This transcription is either prompted by viral or cellular factors. The early gene products are normally regulatory proteins. These proteins regulate the transcription of later genes and viral DNA replication. Later gene products are normally structural proteins required for the construction of new capsids. The late gene products accumulate in the replication site and are eventually assembled into empty nucleocapsids.

Clinical presentation of common oral viral infections
Herpes simplex virus type 1 (HSV-1)
Primary herpetic gingivostomatitis
If the infection occurs in early childhood, the disease is usually subclinical or very mild and is often attributed to ‘teething’. If it occurs at a later age, there are more severe symptoms, with fever, cervical lymphadenopathy and general malaise. Oral manifestations begin with generalized oral discomfort and the development of vesicles most often on the tongue, cheek mucosa and gingivae. These break down to form clusters of small round or irregular superficial ulcers with a yellowish base and a red margin. There is a characteristic widespread inflammation of the gingivae, which appear pinkish-red and swollen (Fig 1). The patient will complain of difficulty with eating and swallowing. This is a self-limiting condition which heals without scarring in about 10 days.1,2
**Herpes labialis**

Secondary herpes simplex lesions (*Herpes labialis*) develop in susceptible people most often at the mucocutaneous junction of the lip or on the skin adjacent to the nostril. The development of these lesions is often preceded by a pricking sensation before blisters form. These blisters then enlarge, coalesce, rupture and become crusted before healing (Fig 2). This usually takes 7-10 days in healthy individuals, but in immunocompromised patients secondary herpetic lesions can be widespread, very slow to heal and refractory to treatment.3,4

**Herpes simplex virus type 2 (HSV-2)**

The natural history of genital herpes indicates that susceptible individuals develop primary infection after their first exposure to either HSV-1 or HSV-2. Genital herpes infections can be associated with serious morbidity. Both HSV-1 and HSV-2 can cause primary genital herpes, with HSV-1 accounting for nearly half of the cases in some centres. In Western countries, HSV-1 rates in childhood are dropping, and many adolescents are infected with HSV-1 as a result of their first exposure to the virus during sexual activity (infection acquired by genital–genital contact or by oral–genital contact).5 Nevertheless, HSV-1 reactivates less frequently from latency in sacral ganglia than HSV-2, so most episodes of recurrent genital herpes are caused by HSV-2. Interestingly, a recent study reported that, of 1388 patients with documented HSV-2 infection, 3.2 per cent had HSV-2 isolated at least once from their mouths and this usually occurred during the first episode of genital HSV-2 or during genital recurrence of HSV-2.6 HSV-2 can cause the initial infection of primary herpetic gingivostomatitis, however it is not known how common this is, nor how common are the recurrent herpes labialis lesions caused by HSV-2.7

**Epstein-Barr virus**

Epstein-Barr virus (EBV) is involved in a diverse range of conditions such as infectious mononucleosis, oral hairy leukoplaikia, non-Hodgkin’s lymphoma, Burkitt’s lymphoma and nasopharyngeal carcinoma. The first two of these conditions will be discussed below.

**Infectious mononucleosis (glandular fever)**

This is a relatively common disease affecting both genders equally and occurring predominantly in teenagers and young adults. There is a relatively long incubation time (35+ days). Transmission is through salivary spread with resultant pharyngitis, lymphadenopathy, malaise, arthralgia and myalgia.

**Oral hairy leukoplakia (OHL)**

This is very uncommon and occurs equally in both genders. It is typically a feature of immunosuppression.
It is characterized by adherent white patches, bilateral, on the dorsum and lateral border of tongue that may extend onto the floor of mouth (Fig 3). The cause of this condition is now thought to be an EBV-related epithelial proliferation that arises due to the associated immunosuppression. Principally, this has been reported in HIV disease, cyclosporin-induced immunosuppression, long-term high-dose corticosteroids use and uncontrolled diabetes mellitus.

**Varicella-zoster virus**

The primary infection of this virus is commonly a childhood illness: chicken pox. This disease has a prodromal illness with oral vesicles and ulcers typically on the palate and a skin rash that can be pruritic, papular and pustular with vesicules that most often occur on the trunk. The disease is self-limiting, lasting 5-10 days and is usually contracted by direct contact. Shingles is the secondary infection of varicella-zoster virus and tends to occur only in middle to late life in both genders. It occurs via viral reactivation and can be associated with immunodeficiency. Typically, this occurs in a dermatomal distribution on the thorax, but can occur facially following the divisions of the trigeminal nerve. When they occur, clinical oral features are unilateral vesicles and ulcers (Fig 4). Ramsay Hunt Syndrome occurs when reactivation involves the chorda tympani, vesicles and ulcers of the external ear (otitis externa), anterior 2/3 tongue, soft palate and facial palsy (Ramsay Hunt Syndrome is rarely bilateral). Postherpetic neuralgia occurs in approximately 30 per cent of patients with shingles and is localized, precipitated by light touch and can be very acute, sharp pain. The involved skin can be erythematous.

**Coxsackie virus**

This virus causes two conditions that involve the oral mucosa.

*Herpangina*

Herpangina is a systemic infection, common in childhood. Fever and sore throat usually last for two days and are followed by the appearance of lesions in the oropharynx. These are numerous small vesicles, 1-2mm in diameter, found mostly on the pillar of fauces,
uvula, tonsils and palate. Unlike herpetic gingivostomatitis, the gingivae are not commonly affected. The oral ulceration will last for three or four days and, unlike herpes infections, there will be no recurrences of that particular type of Coxsackie virus.

Hand, foot and mouth disease

Hand, foot and mouth disease is another Coxsackie virus infection most commonly seen as an epidemic among young schoolchildren. It is characterized by the presence of small vesicles on the oral mucosa, palmar surfaces of the hands and plantar surfaces of the feet. The presence of extra-oral lesions help distinguish it from herpetic gingivostomatitis.

Human papilloma virus

Human papilloma virus (HPV) has been shown to be linked to a number of benign lesions of the oral mucosa, such as squamous cell papilloma, condyloma, verruca and focal epithelial hyperplasia (FEH). The role of HPV in pre-malignant and malignant oral lesions has been a controversial issue. Of the almost 100 known HPV types, at least 25 types have been detected in oral lesions.

Squamous cell papilloma (SCP) is a relatively common benign tumor of the oral epithelium, representing about half of all soft tissue tumors. On gross appearance, oral papilloma are characterized by small finger-like projections, resulting in a lesion with a rough or cauliflower-like verrucous surface (Fig 5). Oral papilloma are benign lesions.

Condyloma acuminatum (venereal wart) is generally regarded as a sexually transmitted disease affecting the skin and mucous membranes of the anogenital tract. It is now accepted that oral condylomas can arise not only by oral sex but also by auto-inoculation or as a result of maternal transmission.

Verruca vulgaris (common wart) is the most prevalent HPV lesion of the skin, but is also found in oral mucosa. The common locations are the mucosal areas in which keratinization of the epithelium resembles that of the skin, i.e., lip, hard palate and gingivae. It has been emphasized that the diagnosis of oral verruca should be preserved for lesions showing histological characteristics of verruca vulgaris of the skin. On clinical examination, verruca is often indistinguishable from SCP and condyloma (Fig 7). To confirm the diagnosis, cutaneous HPV types should be identified in oral verruca. So far, there are no follow-up studies on the natural history of oral verruca.

The term focal epithelial hyperplasia was introduced in 1963 to describe multiple nodular elevations of the oral mucosa observed among American Indians in the United States and Brazil and in an Eskimo boy from Alaska. FEH lesions have now been detected worldwide. FEH appears as multiple, soft, flat or rounded, slightly elevated nodules. The lesions are asymptomatic, their colour ranging from pale to normal as compared to the adjacent mucosa. The lesions may persist for several years, but they tend to regress spontaneously.

Human immunodeficiency virus

The acquired immune deficiency syndrome (AIDS) is the most serious expression of disease resulting from infection with the human immunodeficiency virus (HIV). A diagnosis of AIDS implies that there has been some damage to the immune system resulting in opportunistic infections or secondary cancers. Infection with HIV causes a continuum of clinical conditions. These can range from the asymptomatic carrier state to mild-to-more severe AIDS-related conditions to the diseases of AIDS itself. Mild-to-moderate states encompass a wide spectrum of disease, e.g., OHL, whilst AIDS itself is characterized by more life-threatening infections, neurological manifestations or secondary cancers. Throughout the course of HIV infection, the virus continues to replicate rapidly. CD4 cells, the major cells targeted by HIV, are killed and replaced in large numbers, until, finally, the capacity of the immune system to respond further is exhausted, resulting in severe immunodeficiency.

In Australia, as at 31 December 2002, 77.4 per cent of the 22 548 reported adult HIV cases occurred in homosexual and bisexual men, 11 per cent occurred through heterosexual transmission, 4.4 per cent from injecting drug use, with recipients of blood products or haemophilic constituting 2.8 per cent. HIV spreads by sexual intercourse; injection of blood, or through mucous membranes contaminated with blood or body fluids; and from infected mother to infant – in utero, perinatally and through breast milk. HIV does not spread by casual social contact.

Oral manifestations of HIV infection are OHL, oral candidosis and Kaposi's sarcoma (KS). If it is suspected that patients exhibit any of these conditions and infection with HIV is suspected it is advisable to refer the patient. KS is a common neoplasm in AIDS. Oral involvement may be observed in up to 60 per cent of patients with KS; 45 per cent of patients have both, skin and oral lesions. Oral KS frequently involves the palate, the attached gingivae and the dorsum of the tongue. Clinically, a macular early lesion and a papulo-nodular form are recognized. The aetiology of AIDS-related KS has been extensively investigated, with human herpesvirus 8 (HHV8) being the key agent in the development of this lesion.

Therapeutic use of antiviral agents

Diagnosis

The diagnosis is made most commonly on clinical grounds but a number of special tests are available to provide confirmation. Direct examination of a smear made after scraping a spatula over a lesion will show evidence of viral damage to epithelial cells or immunofluorescence or immunohistochemical evidence of the presence of the virus. Viral culture is a sensitive method which determines precisely which type of virus
is present. Serological demonstration of a rising antibody titer – a fourfold or greater increase in antibody titer to the virus demonstrated between serum obtained in the acute phase of the infection and in the convalescent phase – is diagnostic but depends on obtaining two blood samples approximately a fortnight apart.13

Principles of management

Confirm the diagnosis; check medical considerations (B12/folate/iron deficiency, diabetes, medication, immune deficiency); ensure adequate hydration; Prescribe medication (see below) for pain relief and prevention of secondary infection.14

Pharmacological agents available for treatment

There is, as yet, no medication that prevents HHV1 migrating to the trigeminal ganglion after the primary infection and hence being available for reactivation. Although the antiviral agent Acyclovir has been found to be of benefit in limiting the extent of primary genital HHV2 infections, it has had less effect on orofacial HHV1 primary infections in healthy individuals. However, it does have an important role in the management of primary and secondary HHV1 infections in immunocompromised patients and acute attacks of herpes zoster. Topical Acyclovir is useful for recurrent herpetic infections, but must be started early in the prodromal phase to have a worthwhile effect.11,13

Topical and oral antiviral use have shown modest but statistically significant efficacy in treating herpes labialis with most studies demonstrating a significant reduction in episode length and/or healing time.14 Oral Acyclovir, Valacyclovir and Famciclovir are efficacious and safe for the treatment of the first episode and recurrent genital herpes and are useful as suppressive therapy for individuals with frequent genital herpes recurrences. In addition, high doses of oral Acyclovir, Valacyclovir and Famciclovir have been shown to speed the healing of herpes zoster, and data suggests that these agents also decrease associated acute and chronic pain in people of 50 years of age or older.15

When to refer

When a patient exhibits severe lesions with dehydration, any evidence of ocular or other extra-oral involvement or when they are immunocompromised, they should be referred to either a specialist in oral medicine or an oral maxillofacial surgery. If suspected of extra-oral involvement or dehydration, a patient should be referred to their medical practitioner for further management.

REFERENCES


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