

# VIRUSES IN ORAL DISEASE\*

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**T**he most significant viruses known to cause oral lesions are the herpesviruses, enteroviruses, papillomaviruses and human immunodeficiency viruses<sup>1</sup>.

## HERPES VIRUSES

After primary infection, herpesviruses including herpes simplex viruses (HSV), varicella-zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV) and human herpes virus 6 (HHV-6) may be latent and appear in the saliva from time to time, particularly in immunocompromised persons. Recognisable oral lesions, usually ulcers, can be caused particularly by HSV, VZV and occasionally by CMV and EBV.

### Herpes Simplex Viruses

HSV are the most common herpesviruses to produce recognisable oral lesions<sup>2</sup>.

#### *Clinical features of primary infection with HSV*

Many primary infections with HSV are subclinical or pass unrecognised. The most frequent clinical manifestations are stomatitis and pharyngitis. HSV stomatitis is mainly a childhood infection but is increasingly recognised in adults. The incubation period is 3-7 days.

Primary herpetic stomatitis presents with malaise, anorexia, irritability and fever, anterior cervical lymphadenopathy, and diffuse, purple, boggy gingivitis, especially anteriorly with multiple vesicles followed by round or ovoid ulcers 1-3 mm in diameter scattered across the oral mucosa and gingiva. Stomatitis spontaneously resolves in 7-10 days but the virus remains latent in the trigeminal ganglion. The most obvious sequel is that about one-thirds of patients thereafter are predisposed to recurrences of infection.

## DIAGNOSIS OF PRIMARY HERPETIC STOMATITIS

The diagnosis is mainly clinical. The features of infection (fever, etc) and the oral ulcers with a fairly characteristic gingivitis are highly suggestive.

The patient should be examined to exclude a rash suggestive of chickenpox and the anaemia, bleeding tendency, generalised lymph node enlargement and hepatosplenomegaly suggestive of leukaemia. A full blood picture, white cell count and differential are occasionally indicated.

In immunosuppressed individuals having lesions with an atypical appearance, laboratory testing that can be diagnostically valuable cytological smears which may show multinucleate giant cells, and viral studies such as culture (an oral swab placed in viral transport medium), serology and, rarely, electron microscopy.

## MANAGEMENT OF PRIMARY HERPETIC STOMATITIS

Supportive treatment, particularly maintenance of fluid intake, antipyretics and analgesics (paracetamol) and topical antiseptics (such as aqueous chlorhexidine) to prevent bacterial superinfection are important.

Antivirals are indicated predominantly in immunocompromised patients. Effective antiviral agents, such as acyclovir are available, but strains of HSV resistant to nucleoside analogues are increasingly reported and there is growing evidence of drug resistance in HSV among immunocompromised persons.

## RECURRENT HERPES SIMPLEX INFECTIONS

From time to time, HSV is reactivated and the virus moves down from the trigeminal ganglion along the nerve axons to be released, often asymptotically, into the saliva. Factors that reactivate HSV include trauma, ultraviolet light, fever and immunosuppression. Sometimes, HSV reactivation produces skin lesions, usually at or very close to, a mucocutaneous junction (recurrent herpes labialis: cold sores).

The lesions begin with a prodromal burning

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sensation followed by vesicles which change to pustules before they scab and heal over 7-14 days.

Intraoral secondary "infection" and ulceration with HSV is very rare in healthy patients except sometimes after trauma as, for example, after a local anesthetic injection. However, immunocompromised patients may develop chronic, sometimes severe oral ulceration due to HSV.

#### ***Diagnosis of recurrent herpetic infection***

The diagnosis of recurrent herpetic infection is usually obvious from the clinical features.

Oral ulcers due to HSV can be difficult to diagnose and then material can be sent for culture and (occasionally) electron microscopy. Serology is of no true value in diagnosis.

#### ***Management of recurrent herpetic infection***

- (a) Prevention - Avoidance of factors that cause viral re-activation may reduce the recurrence rate. Barrier creams against ultraviolet irradiation (e.g. Uvistat) may be useful before sun exposure.
- (b) Treatment - Acyclovir is indicated mainly for immunocompromised patients or where there are disfiguring lesions. Few of the other supposed therapies available have been tested in controlled double-blind trials and since there is a significant placebo response, reliable objective data are sparse.

#### ***Erythema multiforme***

Erythema multiforme may affect the mouth alone or in combination with other lesions. Swollen bloodstained lips with widespread oral ulceration are the typical features.

Recent application of the HSV appears to have a role in the majority of cases of recurrent erythema multiforme<sup>3</sup>. These cases can often be controlled by acyclovir. Systemic corticosteroids are often needed in others.

#### **HERPES VARICELLA (CHICKENPOX)**

Chickenpox affects children predominantly. Many primary infections with varicella-zoster virus (VZV) are sub-clinical. The incubation period is 14-21 days.

Chickenpox presents with features that include malaise, anorexia, irritability and fever, mouth ulcers and a centripetal rash that crops. The rash affects the head, neck and trunk mainly and lesions are seen at all stages in development from itchy macules to papules, vesicles, pustules and scabs.

Most patients recover spontaneously in 2-3 weeks but a few develop complications, such as pneumonia. Immunocompromised patients can, however, develop widespread and severe disease.

VZV remains latent, thereafter, mainly in dorsal root (sensory) nerve ganglia.

#### ***Diagnosis***

Diagnosis is usually clinical.

#### ***Management***

Management is supportive in most cases (see above). Antivirals such as acyclovir may be indicated if the patient is immunocompromised.

#### **HERPES ZOSTER (SHINGLES)**

Reactivation of VZV is not common and usually is seen at a late age. Immunocompromised patients are at especially risk from the zoster. The consequent lesions (shingles) are painful and cause extreme distress. Most shingles is in the thoracic region.

#### ***Clinical Features***

If the maxillary or mandibular divisions of the trigeminal nerve are involved features may include:

- (a) Severe pain which often precedes, accompanies and follows the rash (post-herpetic neuralgia) sometimes persisting for months or longer.
- (b) Rash restricted to a dermatome, i.e. the area of skin supplied by a sensory nerve. The rash is unilateral and develops like chickenpox.
- (c) Mucosal ulcers in the distribution of the involved division, i.e. there is ulceration of the ipsilateral tongue, floor of mouth, lower labial and buccal mucosa if the mandibular division of the trigeminal nerve is involved. In maxillary zoster the ulcers involve the ipsilateral palate, upper gingiva, and buccal sulcus.

#### ***Diagnosis***

The diagnosis is usually obvious clinically from the unilateral rash restricted to a dermatome.

#### ***Management***

An underlying immune defect such as HIV disease or malignancy should be excluded. Treatment is mainly supportive but antivirals such as acyclovir may prevent subsequent neuralgia.

#### **ENTEROVIRUSES**

Coxsackie, and sometimes ECHOviruses, can cause relatively minor illnesses, characterised mainly by mouth ulcers. Small epidemics of these infection are not uncommon, particularly in school children.

#### **HERPANGINA**

The incubation period of Herpangina is 3-7 days. Clinical features may include malaise, anorexia, irritability and low fever, anterior cervical lymphadenopathy mouth ulcers on the soft palate predominantly.

Sequelae of any consequence are rare, the

disease resolving spontaneously in 7-10 days.

### **Diagnosis**

There may be a contact history. Diagnosis is usually clinical.

### **Management**

This is supportive only.

## **HAND, FOOT AND MOUTH DISEASE**

Hand, foot and mouth disease is caused particularly by Coxsackie A viruses. The incubation period is 3-10 days. Many infections are subclinical but features of the clinical syndrome may include malaise, anorexia, irritability, fever and anterior cervical lymphadenopathy, occasionally, with sparse round or void mouth ulcers and a painful rash, usually on the hands and/or feet, particularly between digits or at the base of the phalanges.

Diagnosis and management are as for herpangina.

## **HUMAN PAPILLOMAVIRUSES**

Human papillomaviruses (HPVs) are associated with benign proliferations of the skin or mucosae<sup>1, 4</sup>

Several HPV types may infect oral epithelium apparently without necessarily resulting in pathology either at the histological or clinical level. Some HPVs produce lesions and some HPVs may have a role in carcinogenesis<sup>4, 5</sup>

### **HPV-related oral lesions**

HPV are clearly implicated in the aetiology of papillomas, condyloma acuminata, common warts (*verrucae vulgaris*) and focal epithelial hyperplasia<sup>4, 5</sup>

### ***Squamous cell papilloma and condyloma acuminatum***

Oral squamous cell papilloma is a relatively common benign warty lesion, which can occur at any age. HPV6 and HPV11, have been identified in up to 80% of the lesions studied.

Oral condyloma acuminatum (genital warts) are uncommon. They are usually multiple small, white or pink nodules with a surface more cauliflower-like than that of a papilloma. Differentiation from squamous cell papillomas is difficult, and largely

academic. HPV6 and 11 have been found in up to 85% of condylomas.

### **Common wart (*verruca vulgaris*)**

Common warts in the oral cavity are usually firm, whitish, sessile, circumscribed, exophytic lesions, typically on the lips. There is hyperkeratinisation of the superficial epithelium and elongation of the rete ridges which, at the margins usually bend inward towards the centre of the lesions. HPV6, 11 and 16 and cutaneous HPV types e.g. HPV1, 2, 4 and 7 have been found in oral common warts. Indeed, HPV2 and HPV4 have been detected in more than 55% of oral warts.

### **Focal epithelial hyperplasia**

Focal epithelial hyperplasia (FEH) or Heck's disease is a rare benign lesion of the oral mucosa virtually restricted to certain ethnic groups, particularly Eskimos and natural Indians from North and South America. FEH is a manifestation of HPV13 and HPV32 infection in the oral cavity in individuals with a genetic predisposition.

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