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Recurrent Intra-oral Herpes Simplex 1 Infection

Abstract: Human herpes simplex 1 virus (HSV-1) is a DNA virus that has the ability to lie latent and be subsequently re-activated at any point during a patient's life. In the immunocompetent patient, resolution of clinical signs and symptoms usually occurs spontaneously after 14 days. In the immunocompromised patient, healing is often delayed and the effects are much more debilitating. Indications for therapeutic regimes of systemic antiviral treatment are discussed.

Clinical Relevance: Recurrent oral ulceration caused by HSV-1 may be seen by the general dental practitioner and can cause significant morbidity.

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Human herpes simplex virus

The human herpes simplex virus (HSV-1) is a member of the Herpesviradae family (Table 1).[1] All herpes viruses share characteristic architecture, all being close to 200 nm in diameter and consisting of a liquid crystalline DNA core surrounded by a nucleocapsid and envelope.[2] After primary infection, the herpes viruses remain in a repressed latent state in infected cells[3] until re-activated by certain stimuli, including co-infection, eg the common cold, stress, menstruation, hormones, fever, ultraviolet radiation, trauma and immunosuppression.

Epidemiology

HSV-1 is a common cause of infection in the orofacial region and is one of the most common viral infections seen in the general population, with 45–98% of the world population reportedly HSV-1 seropositive.[2,4] Primary infection with HSV-1 is generally acquired in early childhood. Determinant factors influencing infection prevalence include:

- Socioeconomic status;
- Race; and
- Geographic location.[5]

In lower socioeconomic populations in the United States HSV-1 is reported to affect 33% of children aged 5 years and under, compared with 20% in higher socioeconomic groups.[6]

Transmission

Transmission of the HSV-1 is via direct contact with infected lesions and saliva of an individual with active primary or recurrent infection.[5] Following symptomatic infection, viral shedding and transmission

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- Herpes simplex virus 1 – HHV1 – Causes genital ulceration and oral ulceration, but mainly oral.
- Herpes simplex virus 2 – HHV2 – Causes genital ulceration and oral ulceration, but mainly genital.
- Varicella zoster virus – HHV3 – Primary infection causes chicken pox. Re-activation causes shingles.
- Epstein barr virus – HHV4 – Causes Burkitt's lymphoma, infectious mononucleosis, HIV associated hairy leukoplakia, has links with nasopharyngeal carcinoma, and rarely oral ulceration in immunocompromised patients (Figures 1, 2).
- Cytomegalovirus – HHV5 – Causes cytomegalovirus ulceration and retinitis, and has been associated with salivary gland disorders.
- Roseolovirus – HHV6 – Causes exanthem subitum.
- Roseolovirus – HHV7 – Causes exanthem subitum.
- Kaposi's sarcoma-associated herpesvirus – HHV8 – Causes Kaposi's sarcoma.

NB: HHV6 and 7 are not relevant to the dental surgeon's clinical practice.

Table 1. Human herpes simplex viruses.[1]

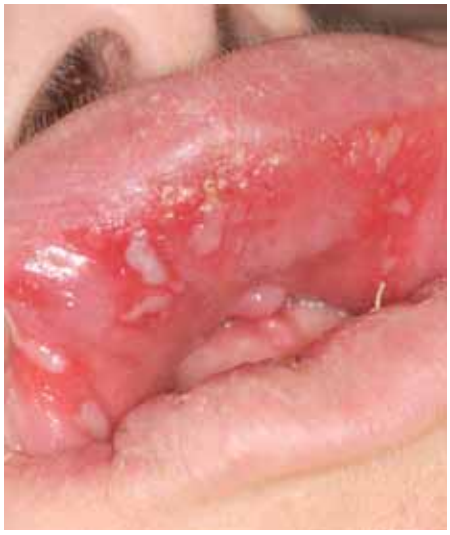

Figure 1. Herpes simplex 1 vesicles and ulceration in an immunocompetent patient.

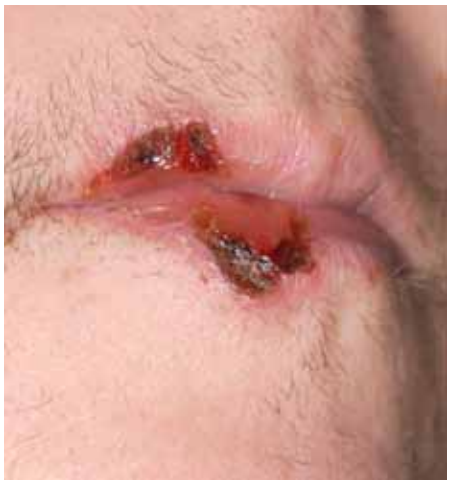

Figure 2. Herpes labialis in an immunocompromised patient.

can occur for several weeks after resolution of symptoms. HSV-1 can remain viable on clothing, skin and plastic for short periods, therefore allowing spread via oral secretions and close non-sexual contact, such as the sharing of kitchen utensils. It is important to be aware that viral shedding can occur in the absence of any symptoms and allow transmission through the same mechanisms detailed above. In contrast, HSV-2 is mainly transmitted by sexual contact.[7,8]

Primary infection

Primary HSV-1 infection refers to the first encounter between HSV-1 and susceptible people, susceptibility being determined by the absence of neutralizing antibodies and specific T-cell immunity against HSV-1.[9] In most cases, primary infections are subclinical and therefore unrecognized.

In clinical symptomatic infection, the most common clinical orofacial manifestation is herpetic gingivostomatitis. The clinical findings observed are those of an acute gingivitis, together with submandibular lymphadenopathy, malaise and fever.[10] In addition, vesicles may develop on the oral mucosa which burst and coalesce to form painful areas of ulceration. It is known that many primary cases occur in childhood and anecdotally that symptoms are often put down to teething.

In the immunocompetent patient clinical primary infection usually resolves spontaneously within 14 days (Figure 1). Viral shedding can continue for several weeks, due to lysis of the infected host cells releasing herpes simplex virions.[11]

Secondary infection causing recurrent oral ulceration

HSV-1 is able to re-activate after lying latent for a period of time. Re-activation is stimulated by several factors, including co-infection, eg the common cold, stress, menstruation, hormones, fever, ultraviolet radiation, trauma and immunosuppression. It is thought that the location of the latent virus is in the sensory nerves reaching the area of initial inoculation; in the case of the oral mucosa and peri-oral area, this is the trigeminal nerve, specifically the trigeminal nerve ganglion. Reported rates of recurrence of oral HSV-1 infection are variable, from 16–45%.[12] Re-activation may result in clinical manifestations such as herpes labialis (Figure 2), intra-oral ulceration, and recurrent intra-oral herpes ulceration (RIOHU). However, most recurrences in the healthy person are asymptomatic and go undetected but still result in asymptomatic shedding of the virus. Although this article focuses on intra-oral ulceration, the overall majority of symptomatic re-activation manifests as herpes labialis.

Re-activation is clinically significant, both in terms of transmission and as an aetiological factor, in association with conditions such as cranial nerve palsies and erythema multiforme.[13]

Herpes-associated erythema multiforme (HAEM)

Erythema multiforme (EM) is an acute hypersensitivity reaction mainly mediated by cytotoxic lymphocytes causing keratinocyte necrosis with potential involvement of mucosa and skin. EM can differ in extent of involvement; from one mucosal site, to erosions involving the oral mucosa and lips. Steven-Johnson Syndrome is a more severe form of EM, with widespread skin, genital, and eye involvement which may sometimes be fatal.[14]

EM may recur and, indeed, 80% of recurrent EM minor cases may be associated with HSV re-activation, either in the form of asymptomatic shedding or overt recurrent infection (HAEM).[15]

Recurrent intra-oral herpes ulceration (RIOHU)

RIOHU presents with prodromal symptoms, such as tingling or a burning sensation followed by vesicle formation within an area of a sensory nerve distribution. Unilateral ragged ulceration with surrounding erythema is observed. Compared with primary infections, recurrent episodes are shorter in duration, less severe, and there is reduced systemic involvement, however, they are still accompanied by pain, mainly of a burning character and still represent a transmission risk.[16,17]

The immunocompromised patient

This patient group includes patients with AIDS, recipients of bone marrow and organ transplants, patients undergoing chemotherapy or radiation therapy, and patients whose medication causes iatrogenic immunosuppression. Recurrent HSV infections in these patients may be frequent and severe, with sizeable lesions involving both keratinized and non-keratinized mucosa[10,18] In the pre-antiviral drug era, such infections were responsible for fatal complications.[13] The symptoms caused by RIOHU in these patients can

cause considerable pain and discomfort. In addition, they are more at risk of superinfection with bacteria and fungi.[19]

HSV-2 and recurrent intra-oral herpes ulceration

Primary and recurrent oral infections with HSV-2 are rare and generally occur in association with genital herpes infection**.** The clinical appearance of HSV-2 recurrence within the oral cavity may be very similar to HSV-1 induced ulceration.[20–22] Oral shedding of HSV-2 may occur in association with primary or recurrent genital infection, even when oral lesions are clinically absent.[23] However, the transmission risk in the absence of sexual contact is minimal.[24]

Discussion and overview of management of recurrent intra-oral herpes ulceration

Diagnosis

Diagnosis is usually based on the clinical history and extra-oral and intra-oral examination. Precipitating factors and the patient's immune status should be noted. A characteristic history of systemic symptoms, with acute gingivitis and painful ulceration of the oral mucosa, are suggestive of primary HSV-1 infection. Repeated episodes of intra-oral ulceration on the hard palate and keratinized gingivae, and ulceration on the outer vermillion border, following a tingling or burning sensation in that area, suggest RIOHU.

RIOHU may be mistaken for other conditions, notably the herpetiform form of recurrent aphthous stomatitis and recurrent erythema multiforme.[25,26] A number of potential causes of recurrent oral ulceration are listed in Table 2 and may need to be considered in the differential diagnosis, however, further elaboration is outwith the scope of this article.

Broad classification category of cause	Example
Idiopathic	Recurrent aphthous stomatitis
Infective	RIOHU, intra-oral herpes zoster induced ulceration
Drugs	NSAIDs, Alendronate, Nicorandil
Immunological	Recurrent erythema multiforme
Constitutional (associated with systemic disease)	Inflammatory bowel disease, Behçet's syndrome, Cyclic neutropenia.

Table 2. Causes of recurrent oral ulceration.

Investigations

Investigations can provide confirmation when clinical doubt exists. Laboratory confirmation becomes particularly important in cases of recurrent infection, especially in the presence of immunosuppression. In a hospital setting, the laboratory investigations outlined below may help confirm the clinical diagnosis.

Viral DNA detection by polymerase chain reaction

Vesicle fluid may be aspirated, although this can be difficult within the oral cavity. Alternatively, a swab can be taken from a ruptured vesicle and sent to the laboratory in appropriate transport medium for PCR analysis. This is the most sensitive method for viral diagnosis of HSV-1.[27]

Serological assays

Serological assays examine the presence of antibodies. An acute serum confirmed by anti-HSV IgG with a four-fold rise in titre three weeks later, together with the appearance of HSV specific IgM, may be diagnostic of a recurrent HSV infection. The usefulness of this test is limited as only a small proportion of patients with recurrent infection exhibit a significant rise in titre.[28,29] Serology should not be considered the investigation of choice in the diagnosis of recurrent HSV infection and should only be considered when other investigations, such as culture or PCR, are not available or feasible as first line investigations.[2]

Culture

Vesicle fluid is swabbed and cells are inoculated with the sample. Viral-induced changes in the cells, such as enlarged nuclei and multinucleated giant cells, indicate viral infection. Monoclonal antibodies to HSV-1 can be used to detect viral antigens. This method is commonly used as it is a simple, inexpensive and fast way of effectively detecting HSV.[2]

Cytological smear and Tzanck test

A smear is taken from the base of a freshly broken vesicle. Papanicolau or Wright's stain is applied to the sample which is then examined with light microscopy, noting the presence of virus damaged cells. This method cannot differentiate between HSV-1 and HSV-2 and has an overall low rate of infection detection.[2]

Biopsy

This investigation is only indicated if the presentation is unusual and a biopsy has been carried out for diagnostic purposes. Histopathological examination will show degenerative changes in cells owing to the presence of HSV-1. If the tissue is fixed, immunohistochemistry may confirm diagnosis, whilst on fresh/frozen tissue PCR can be applied for increased sensitivity.

The recommended diagnostic sample is a lesional swab which is sent for PCR to HSV in viral transport medium. Serology is not the optimal test for RIOHU as IgM may be negative, especially in re-activation.[30]

Management of recurrent intra-oral HSV-1 ulceration

In the immunocompetent patient, healing of oral ulceration is usually spontaneous and occurs within 10–14 days. In the presence of immunodeficiency, the clinical course may be more severe and the potential complications greater, therefore systemic antiviral therapy should be considered immediately. Education about transmission risks should be considered

- Immunocompetent patient
- Localized and accessible lesions
- Outbreaks are infrequent and limited in severity

Table 3. The relative indications for use of topical intermittent antiviral therapy in RIOHU.

- Severe outbreaks
- Immunosuppression
- Multiple lesions
- Inaccessible location for topical treatment
- Frequently recurring lesions

Table 4. The relative indications for use of systemic antiviral therapy in RIOHU.

within the context of the patient's family, social and sexual circumstances.

Various treatment regimes are seen in the literature and in practice. They can be simplified by dividing them into two categories:

- Intermittent therapy; and
- Chronic suppressive therapy.[31]

Intermittent therapy

This is indicated in patients suffering from isolated symptomatic episodes. Isolated, infrequent, mild attacks may simply require symptomatic treatments, such as topical analgesics, eg benzydamine hydrochloride mouthwash. However, frequent and severe disease, or significant patient distress are indications for the introduction of antiviral therapy. Treatment is most successful if begun within 48 hours of the start of the episode. Evidence for the effectiveness of topical antiviral creams varies, however, some studies have shown topical aciclovir 5% and penciclovir 1% cream to decrease lesion healing time and lesion severity (Table 3).[32] Systemic treatments shown to reduce lesion healing time and reduce pain are aciclovir 200–400 mg 5 times a day for 5–7 days, or valaciclovir 1 g twice daily for 3–5 days (Table 4).[30,33]

Chronic suppressive therapy

This is essentially long-term prophylactic treatment. In a systematic review of treatment and prevention of HSV in patients undergoing treatment for cancer, both aciclovir and valaciclovir reportedly reduced healing time, relieved pain, reduced the duration of viral shedding, and prevented symptomatic infections. Both drugs were equally effective.[34] The advantage of valaciclovir is that it has a longer half life and can, therefore, be taken less frequently than aciclovir, resulting in increased compliance.[2] Woo *et al* suggested a therapeutic regime of aciclovir 400–800 mg 3 times a day or valaciclovir 500–1000 mg 2 times a day.[33] In practice, the lowest dose at which control of disease is achieved varies between patients and hence flexibility in dosing is paramount.

The authors are not aware of any randomized controlled trials involving chronic suppressive therapy using famciclovir to prevent intra-oral recurrence of HSV-1.

There is evidence, from randomized controlled trials,[35–37] for the efficacy of famciclovir in preventing genital herpes and recurrent episodes of labial herpes, with consequent inferred efficacy for use in the prevention of intra-oral recurrence (Table 5).[31,38]

Case report

Herpes simplex virus 1 intra-oral ulceration in a patient with rheumatoid arthritis

This report details a case of oral ulceration caused by the HSV-1 in a patient being treated for rheumatoid arthritis with methotrexate. It highlights the potential debilitating oral side-effects of opportunistic infection caused by methotrexate-induced immunosuppression.

Case report

A 67-year-old lady was referred urgently to Newcastle Dental Hospital by her general dental practitioner with oral ulceration and an intense burning pain which was progressively increasing in intensity, despite taking therapeutic doses of diclofenac (NSAID), and which had started six days previously. Her oral symptoms were accompanied with fatigue and malaise. Her medical history included stable angina and rheumatoid arthritis, for which she was taking methotrexate (25 mg/week). Clinical examination revealed unilateral painful oral ulceration involving the left hard and soft palate (Figure 3). The clinical findings were consistent with a differential diagnosis of intra-oral HSV ulceration or varicella-zoster virus (VZV) ulceration. Empirical treatment with valaciclovir 1 g twice daily, gabapentin 900 mg daily and lignocaine lollipops were prescribed as systemic and topical pain relief, respectively. As the pain was of an

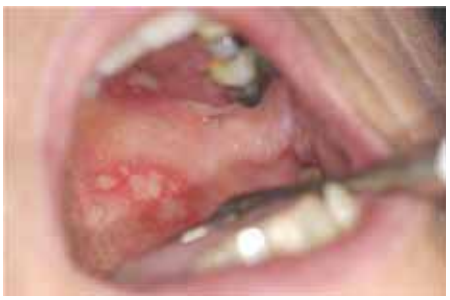

Figure 3. Palatal ulceration on presentation.

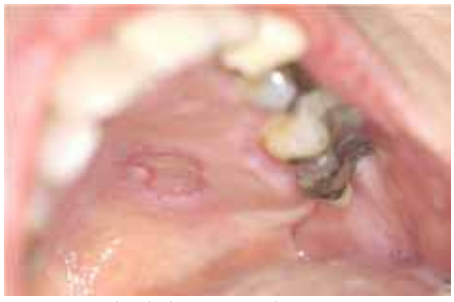

Figure 4. Palatal ulceration at later presentation.

- Severe, frequent attacks in immunocompetent patients
- RIOHU in immunocompromised patients

Table 5. Relative indications for chronic suppressive therapy.

unrelenting severe, constant and burning quality and unresponsive to NSAIDs, it was postulated that it was partially secondary to neuropathic pain induced by the herpes simplex infection.

Gabapentin, which has proven efficacious in the management of neuropathic pain, such as post-herpetic neuralgia, was prescribed to target this neuropathic pain, with immediate positive results.[39]

The lignocaine lollipops used by the patient are manufactured by the regional 'Specials' pharmacy, with the active ingredient being 100mg lignocaine. They contain: granulated sugar, liquid glucose BP, lidocaine hydrochloride BP 100 mg, water for injection, lemon spirit BPC, and olive oil (refined) BP. The lollipops can be rubbed into the painful ulcerated area, providing a user friendly method of delivering topical anaesthesia.

A lesional swab was taken and sent for PCR to HSV and VZV and results were rapidly available in 4 days. This revealed a positive result for HSV-1, negative for HSV-2 and VZV. A venous blood sample was sent for viral serology. The diagnosis was discussed with the patient's rheumatologist and methotrexate was temporarily stopped until the ulcers had healed. This treatment regime was continued for 2 weeks until the ulceration had resolved with complete resolution of her pain.

Unfortunately, the ulceration recurred one month later after restarting methotrexate therapy, with identical site involvement and presentation (Figure 4). The same treatment regime was prescribed on an empirical basis. Following healing of the ulcer, she was prescribed prophylactic valaciclovir 500 mg daily with instructions to increase the dose and contact the Department if further ulceration developed. Any attempt at discontinuation of the prophylactic antiviral medication resulted in a recurrence of the ulceration and it was therefore decided to continue with valaciclovir 500 mg daily as chronic suppressive therapy. Her medication was changed from methotrexate to leflunomide by her rheumatologist. However, we were unable to discontinue her prophylactic antiviral therapy without a recurrence of herpetic ulceration. She remains on this treatment regime with optimal control of her ulceration.

Discussion

Recurrent intra-oral HSV ulceration is potentially debilitating in immunocompetent individuals but more so in the immunocompromised patient. Methotrexate has become increasingly employed in low doses (5–25 mg/week) as *disease modifying anti-rheumatic drugs* (DMARDs) in the management of rheumatoid arthritis. Methotrexate has a substantial clinical benefit in the treatment of patients with rheumatoid arthritis and may be used as an alternative to systemic steroids, avoiding the side-effects seen with long-term steroid treatment.[40,41] Systemic side-effects of methotrexate include liver, renal and bone marrow toxicity, and immunosuppression-related complications. Reported oral side-effects include oral ulceration and mucositis. Singh *et al*[42] found that, out of the DMARDs, methotrexate was most likely to cause oral ulceration, however, this may be more common with high dose methotrexate and may be due to folate deficiency, simultaneous use of other antifolate drugs, or dosage error.[43] Opportunistic recurrent HSV-1 infection and, by inference, considering the main predisposing factor which is that of immunosuppression, recurrent VZV oral ulceration needs to be considered in the differential diagnosis, even in patients on low dose methotrexate, as in this case.[44]

Introducing antiviral drug regimes may reduce the morbidity of the HSV-1, particularly in immunocompromised patients.[39] In this case, prophylactic suppressive therapy with valaciclovir was given and methotrexate temporarily stopped. This successfully prevented the patient suffering from recurrent herpes infection and resultant intra-oral ulceration.

Summary

Patients with RIOHU may present initially to their general practitioners. They should be aware of the potential differential diagnoses and also management and treatment options.

Acknowledgements

Figure 3 has been previously published in 'Diagnosis and management of oral mucosal lesions in older people: a review' *Reviews in Clinical Gerontology* 2008; **18**(2): 115–128. This figure has been adapted from and published under permission from the copyright holders, Cambridge University Press.

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CPD ANSWERS

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1. B, C	**6.** B
2. B, C, D	**7.** A, B
3. A, B, C, D	**8.** B, D
4. A, C	**9.** A, C, D
5. A, C, D	**10.** C