Asian Journal of Modern and Ayurvedic Medical Science | ISSN 2279-0772

[ONLINE]Volume: volume1,number 1 |publication Date: Sunday, July 01, 2012,Published by Mpasvo [article url

http://www.ajmams.com/viewpaper.aspx?pcode=73e3bf9a-d980-4b62-b53d-a5d44d98901a

Published Research Paper's Title : Oral ulcers and its relevance to systemic disorders – A Review

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Asian Journal of Modern and Ayurvedic Medical Science (ISSN 2279-0772) Vol.1,no.1, July 2012.[©The Author 2012]

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A Review Article

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Oral ulcers and its relevance to systemic disorders – A Review

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Declaration

The Declaration of the authors for publication of Research Paper in Asian Journal of Modern and Ayurvedic Medical Science (ISSN 2279-0772 Rajul vivek 1 , Ankita Singh 2 , T.P.Chaturvedi 3 and Ajai Gupta 4 ,the authors of the research paper entitled Oral ulcers and its relevance to systemic disorders – A Review declare that , We take the responsibility of the content and material of our paper as We ourself have written it and also have read the manuscript of our paper carefully. Also, We hereby give our consent to publish our paper in ajmams , This research paper is our original work and no part of it or it's similar version is published or has been sent for publication anywhere else.We authorise the Editorial Board of the Journal to modify and edit the manuscript. We also give our consent to the publisher of ajmams to own the copyright of our research paper.

Received january 15,2012;accepted june 5, 2012 ,published july1,2012

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ABSTRACT : Oral ulceration is a common problem, and is sometimes a marker of gastroenterological disease. Patients with signs or symptoms of oral ulcers are sometimes referred to gastroenterology clinics, however, in most instances the ulcers does not reflect gastrointestinal disease. Indeed, a spectrum of disorders other than those of the gut can give rise to oral mucosal ulcers ranging from minor local trauma to significant local disease such as malignancy or systemic illness. This present article reviews aspects of the aetiology, diagnosis and management of common ulcerative disorders of the oral mucosa

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INTRODUCTION

Oral ulcers is a very common disorder of the oral mucosa. Several predisposing factors have been suggested and oral ulcers can be a feature of various systemic disorders including inflammatory bowel disease. The nature, site, duration and frequency of oral ulcers are determined by the underlying systemic condition. In addition, usually histopathological examination warrants a definitive diagnosis in the majority of conditions described in this paper. Clearly, it is not possible to discuss all oral conditions giving rise to oral mucosal ulcers; hence, the present article will focus on ulcerative disorders either of general clinical significance, or relevant to gastroenterology.

ORAL ULCERS TRAUMATIC AETIOLOGY

Most traumatic ulcers of the mucosa are due to physical trauma. In addition, ulcers

may arise with local application of aspirin,[1] cocaine or smoking crack cocaine (e.g. on the palate).[2] Snorting cocaine may rarely cause necrosis, possibly associated with ischaemia, at the floor of nose and eventual ulcers of the hard palate and oronasal fistula formation.[3] Local radiotherapy and some cytotoxic chemotherapy regimes can cause oral mucositis. This manifests as multiple areas of painful mucosal erythema, ulcers and sloughing.[4] The precise aetiology of the mucositisremains unclear, although most likely reflects a loss of basal cell proliferation[5] rather than a reaction to changes in the local oral microflora (e.g. rises in Gram-negative bacteria, particularly Enterobacteriaceae). [6] This mucositis, akin to that of the bowel, is difficult to manage specifically. Benzydamine hydrochloride mouthrinse or spray may provide symptomatic relief, but often effective analgesia requires opioids. The clinical feature of oral mucositis does not significantly improve with topical chlorhexidine gluconate, although this is commonly used in clinical practice. Novel regimes for the treatment of mucositis include granulocyte- macrophage colony-stimulating factor (GM-CSF) and protegrins, although these are presently in the stages of clinical trial.[7, 8]

.VIRAL DISEASES: HERPES SIMPLEX INFECTION

A wide range of infections can give rise to oral ulcers. Primary herpes simplex type 1 (HSV-1) remains the most common viral precipitant of ulcers. Affected individuals may have widespread, small, superficial ulcers of the oralmucosa . The gingiva are often swollen and ulcerated, giving rise to features akin to acute necrotizing ulcerative gingivitis (ANUG) (see below). While previously regarded as a disease of childhood, often primary HSV-1 infection arises in the second or third decade of life.[9] Severe and/or recurrent HSV-1 infection sometimes presenting atypically may be suggestive of underlying immunodeficiency, in particular lymphoproliferative disease or HIV disease.[10] Therapy typically comprises symptomatic relief, although systemic aciclovir and other anti-virals should be considered when disease is severe, recurrent or atypical.[13] Aciclovir resistance may arise in immunosuppressed patients receiving repeated therapy, hence the need for famciclovir, valciclovir or foscarnet.[11]

Herpes simplex virus 2

Although uncommon, HSV-2 can give rise to oral ulcers akin to that of mild primary HSV-1 infection. This oralulcers arises as a consequence of orogenital transmission of the causative virus.

Epstein–Barr virus

Ulcers caused by Epstein–Barr virus (EBV) is rare, but may be a feature of infectious mononucleosis. The ulcers comprises a few small superficial ulcers of the oral mucosa. EBV is more typically associated with the ulcers of some non-Hodgkin's lymphomas[12] or white patches termed oral hairy leukoplakia (OHL) that may arise in immunodeficiency (e.g. HIV disease, corticosteroid or other systemic immunosuppressant therapy, etc.). Of relevance, OHL has been observed in patients with inflammatory bowel disease receiving immunosuppressive regimes.[13]

Cytomegalovirus

Cytomegalovirus (CMV) may give rise to large, chronic ulcers of the oral mucosa or gingiva.[14] These CMVrelated ulcers occur exclusively in significant immunodeficiency, notably severe HIV disease. The diagnosis of such ulcers is difficult and is often only confirmed by resolution of ulcers with ganciclovir therapy.[15]

Human herpesvirus 8 (Kaposi's sarcoma herpes virus)

Human herpesvirus 8 (HHV-8) is the cause of Kaposi's sarcoma (KS), a lesion commonly arising within the mouth of patients with severe HIV disease or a feature of profound iatrogenic immunosuppression (e.g. in patients with inflammatory bowel disease). Oral KS typically affects the palate or gingiva and manifests as red, blue or purple macules, papules, nodules or ulcers.[16] Confusingly, oral KS may occasionally be non-pigmented, and hence may mimic SCC.[17]

Human immunodeficiency virus

The oral consequences of HIV disease are reviewed in detail elsewhere.[18,19] Infection with HIV gives rise to a wide spectrum of oral ulcerative lesions. The majority of these are detailed in other sections of the review. A minority of patients with severe HIV disease can develop deep, necrotic ulcers of unknown aetiology . These ulcers are painful, cause profound dysphagia and/or dysarthria and can arise on any oral mucosal surface, although the buccal and pharyngeal mucosae are the more commonly affected sites. The precise aetiology of these HIV-related ulcers is unknown.[20] HHV-8 DNA has been detected within these, although whether the virus is causative or merely a passenger remains unclear.[21] Of note, the ulcers typically resolve with systemic thalidomide (e.g. 200 mg daily) perhaps reflecting an antitumour necrosis factor (TNF)-a effect in keeping with a viral aetiology.[22] Small number of patients with HIV disease may have ulcers similar to that of recurrent aphthous stomatitis (RAS), although whether the frequency of RAS in HIV is truly increased remains unclear.[23]

BACTERIAL INFECTION

Acute necrotizing ulcerative gingivitis

Acute necrotizing ulcerative gingivitis (Vincent's disease, trench mouth, acute ulcerative gingivitis) is a nonspecific ulcerative disorder almost always localized to the gingivae.[24] Associated contributing factors include poorly controlled diabetes mellitus, tobacco smoking, immunodeficiency (notably severe HIV disease) and possibly psychological stress. Acute necrotizing ulcerative gingivitis manifests as painful ulcers of the gingival margins, particularly the interdental areas. The ulcers may be localized or generalized and when severe will give rise to cervical lymphadenopathy and very rarely pyrexia and malaise. There is often oral malodour. Long-standing or recurrentdisease may lead to destruction and loss of interdental papillae. An ANUG-like disease termed cancrum oris (noma) can arise in profoundly malnourished children and adults. Unlike the ANUG in immunocompetent individuals, the ulcers of cancrum oris spreads to the adjacent soft tissues leading to necrosis of the lips and/or cheeks. Cancrum oris has most commonly been reported in children in Central Africa, the malnourishment arising from poverty because of political and economical unrest.[25] An ANUG-like disorder which spreads to the underlying bone and adjacent soft tissues – termed necrotizing stomatitis – has been reported in a small number of patients with severe HIV disease. Occasionally, this disorder may be the first, and/or only clinical manifestation of HIV disease.[26] The ulcers of the ANUG typically resolves with the removal of deposits of plaque and calculus and the topical application of chlorhexidine gluconate mouthrinse (0.2%) or gel (1%). Systemic antimicrobials (e.g. metronidazole or phenoxymethyl penicillin) may be required when the gingival is profound and/or there is systemic upset. Cancrum oris additionally requires tissue debridement and correction of the underlying malnourishment, however, the prognosis of affected children is often poor.[27]

Posthealing fibrosis and scarring is a significant complication of cancrum oris.

Treponema pallidum

The frequency of oral ulcers because of infective syphilis is likely to increase as a consequence of the rising number of subjects affecting with Treponema pallidum.[28] Oral ulcers can arise in primary, secondary or tertiary disease. In primary disease, a chancre can develop on the oral mucosa as a consequence of direct contact with an infective lesion. The ulcers of primary infection typically arises on the upper (in females) or lower lip (in males) and manifests as a superficial to deep isolated ulcer sometimes with a rolled edge. Occasionally, there can be isolated ulcers of the gingiva.[29] The oral chancre typically resolves with antimicrobial therapy.[30] Secondary syphilis can give rise to multiple areas of superficial papules and ulcers, some of the latter being serpiginous and thus termed snail-track ulcers. Tertiary disease may produce ulcers as a consequence of gumma formation, the ulcers manifesting as isolated areas of chronic ulceration sometimes with the destruction of the underlying soft and/or hard tissues (e.g. palate or tongue).

IDIOPATHIC ULCERS

Recurrent aphthous stomatitis

Recurrent aphthous stomatitis is the most common non-infectious and non-traumatic oral mucosal ulcerative disorder. It is characterized clinically by recurrent bouts of oral mucosal ulcers in an otherwise well subject. The ulcers arises every 4–12 weeks and may be classified as minor, major and herpetiform . The ulcers are superficial, rounded and have a yellow coloured slough with surrounding erythema. The ulcers of major RAS may cause scarring on healing, and it has been suggested that the ulcers of herpetiform RAS may coalesce to produce large areas of ulcers that heal with scarring. Rarely major aphthous stomatitis may cause tissue destruction (e.g. of the soft palate). Undoubtedly RAS has an immunologically mediated pathogenesis but the precise cause of RAS remains unclear.[31] Suggested aetiologies, include idiopathic haematinic deficiency, cessation of tobacco smoking and psychological stress, but there is little scientific evidence in support of any of these. While superficial ulcers similar to RAS may arise in gluten-sensitive enteropathy,[32] the vast majority of patients with RAS have no clinical, gastroenterological or serological features of this small bowel disorder. To date nocommon viral or bacterial infection of the mouth has There is no consistent association between Helicobacter pylori infection and RAS.[33] The treatment of RAS remains unsatisfactory. Therapy is directed towards reducing the duration and/or frequency of ulcers.[34] The mainstay of therapy is topical corticosteroids, however, few of these have been found to be significantly effective in appropriate clinical studies. Chlorhexidine gluconate mouthrinse may be of some benefit (and has been evaluated in detail), but it really has limited clinical value in the management of RAS. Benzydamine hydrochloride spray or mouthrinseprovides some symptomatic relief but does not hasten ulcer healing. Although effective, systemic therapy with prednisolone is rarely warranted, while the role of immunosuppressants is unclear. Thalidomide is highly effective but in view of the adverse side-effects of teratogenicity and neurotoxicity its routine application for such a recurrent and minor disorder is contraindicated.

ORAL ULCERS RELATED TO SYSTEMIC DISEASE

Gastrointestinal disease

Gluten-sensitive enteropathy. Superficial oral mucosal ulcers similar to RAS may be a feature of 1–5% patients with undiagnosed, untreated gluten-sensitive enteropathy. [35] The ulceration is presumably due to the associated haematinic deficiencies.

Dermatitis herpetiformis and related disorders

Oral lesions in dermatitis herpetiformis have been rarely described. These may comprise oral mucosal vesicles, blood-filled blisters, irregular ulcers and desquamative gingitivitis. Linear IgA disease may likewise give rise to blood-filled vesicles or bullae, irregular ulcers and desquamative gingivitis.[36]

Crohn's disease and related disorders

Oral ulcers arises in approximately 9% of patients with undiagnosed Crohn's disease and can be the first and/or only clinical features of this disorder.[37] Two types of oral ulcers can arise in orofacial granulomatosis (OFG) and Crohn's disease – chronic deep linear ulcers, usually of the buccal vestibules, which often have a rolled edge because of mucosal tags, and superficial oral mucosal ulcers presumably because of haematinic deficiency. The diagnosis of such ulcers requires establishing the presence of non-caseating granulomas and the exclusion of other granulomatous disease such as sarcoidosis .

Ulcerative colitis

Ulcerative colitis can give rise to either aphthous ulcers or multiple pustules termed pyostomatitis vegetans. The ulcers of the latter arise on the upper and lower anterior vestibules, the soft palate and posterior hard palate. Pyostomatitis vegetans tends to arise in patients with undiagnosed or active ulcerative colitis. Although most frequently associated with ulcerative colitis, pyostomatitis vegetans may occasionally arise in Crohn's disease.[38] Pyoderma gangrenosum, manifesting as a solitary, necrotic mucosal ulcer has rarely been reported in the mouth.

DERMATOLOGICAL DISEASE

Lichen planus

Lichen planus is by far the most common dermatological disorder to give rise to oral ulcers. Lichen planus is an immunologically mediated disorder histopathologically characterized by an intense dermal infiltrate of T-lymphocytes. The precise trigger for this immunological reaction is unclear. There is no evidence that the clinical features of idiopathic oral lichen planus are any different to those of drug-associated disease.[39] Drugs that may commonly give rise to lichen planus-like disease include sulphonyureas, non-steroidal anti-inflammatory drugs, b-blockers, antimalarials, penicillamine and gold. Associations between hepatitis C virus and oral lichen planus probably reflect the epidemiology of hepatitis C virus infection and/or use of interferon-a.[40] are having painful symptoms and/or there are signs of erosion, ulcers or blister formation. Typical treatment comprises topical corticosteroids,[41] although severe disease may warrant local (e.g. topical tacrolimus) and systemic immunosuppressant therapy..

MALIGNANCY

The most common tumour of the mouth, and typically manifests as a solitary ulcer of the dorsum of tongue or floor of mouth. The ulceration is locally destructive and when affecting the tongue may give rise to lingual and/ or hypoglossal nerve damage with or without dysarthria or dysphagia. Gingival SCC may give rise to tooth mobility and very rarely a

pathological fracture of the mandible. Oral SCC remains one of the more common cancers worldwide, particularly in developing countries such as India.

Non-Hodgkin's lymphoma

Non-Hodgkin's lymphoma may manifest as a solitary area of necrotic ulcers typically affecting the gingiva, palate and fauces. This tumour may arise de novo but often is associated with iatrogenic immunosuppression in HIV disease. A detailed review of non-Hodgkin's lymphoma of the mouth can be found elsewhere.[42] NK/ T-cell lymphoma tends to affect the upper anterior gingival and palate; this is a T-cell lymphoma in contrast to most non-Hodgkin's lymphoma of the mouth.

CONCLUSION

The present article has presented an overview of the common clinical presentations of oral ulceration. Gastrointestinal disease, particularly undiagnosed glutensensitive nteropathy, Crohn's disease and ulcerative colitis, can give rise to ulcers of the mouth. However, these and other gut diseases can give rise to a range of other oral features , hence, it is important to ask patients who present with gastrointestinal disease about their symptoms and to examine the mouth.

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