Chronic ulcerative stomatitis: a distinct clinical entity?

SADJ April 2011, Vol 66 no 3 p119 - p121

J Fourie: *BChD, MSc Odont*, University of Pretoria, School of Dentistry, Department of Periodontics and Oral Medicine.
WFP van Heerden: *BChD, MChD (Oral Path), PhD, FC Path(SA) Oral Path, DSc*, University of Pretoria, School of Dentistry, Department of Oral Pathology and Oral Biology.
SC McEachen: *MChD (MaxFac Oral Surg), FDS RCPS (Oral Med)*, University of Pretoria; School of Dentistry, Department of Oral Pathology and Oral Biology.
A van Zyl: *BChD, MChD (OMP)*, University of Pretoria, School of Dentistry, Department of Periodontics and Oral Medicine.

Corresponding author
J Fourie: University of Pretoria, School of Dentistry, Department of Periodontics and Oral Medicine. PO Box 1266, Pretoria 0001. Tel: 012 319 2426. Fax: 012 326 3375. E-mail: jeanine.fourie@up.ac.za.

SUMMARY

Chronic ulcerative stomatitis (CUS) is a mucocutaneous disorder which is characterised by persistent oral mucosal ulceration. The clinical appearance is often reminiscent of oral lichen planus (OLP) leading to erroneous diagnoses. The immune mediated inhibition of the CUS protein (CUSP) is implicated in the pathogenesis of CUS. CUSP acts as an anti-apoptotic protein and when its action is prevented it may result in significant epithelial injury.

The objective or this article is to present the first documented case of CUS in South Africa, with relevant reference to current international literature. CUS should be considered in patients previously diagnosed with OLP but who are unresponsive to glucocorticosteroid therapy. The condition can be successfully managed using hydroxychloroquine.

INTRODUCTION

Chronic ulcerative stomatitis (CUS) was first described by Jaremko *et al*, (1990),[1] and has subsequently been reviewed in another 39 patients by Islam *et al*, (2007).[2] Most of the 39 reported cases occurred in elderly females. Patients with CUS present with widespread oral ulceration that is often bordered by white striations as is seen in oral lichen planus (OLP).[2] CUS may therefore easily be mistaken for OLP.

CUS can be distinguished from other immune mediated vesiculo-ulcerative conditions by its very characteristic direct immunofluorescence (DIF) pattern.[1] This distinction is necessary because, unlike other immune mediated conditions, CUS is generally not responsive to glucocorticosteroids. Instead, CUS reacts favourably to hydroxychloroquine.[2]

In this article we report on the first case of CUS published in South Africa. This case was complicated by the concurrent presence of skin lesions. A review of the literature will highlight the features of CUS as it relates to the diagnosis and management of the condition.

CASE HISTORY

A 42-year-old female presented to the Oral Medicine Clinic, Pretoria Oral and Dental Hospital, with the main complaint of oral pain and ulceration of three months duration. Her medical history included a pruritic rash and crusting ulcers on her body and an ulcer of her right foot of 13 years duration. She gave a history of lesions of the vaginal mucosa. She was being treated with amitriptyline and diazepam for depression and anxiety.

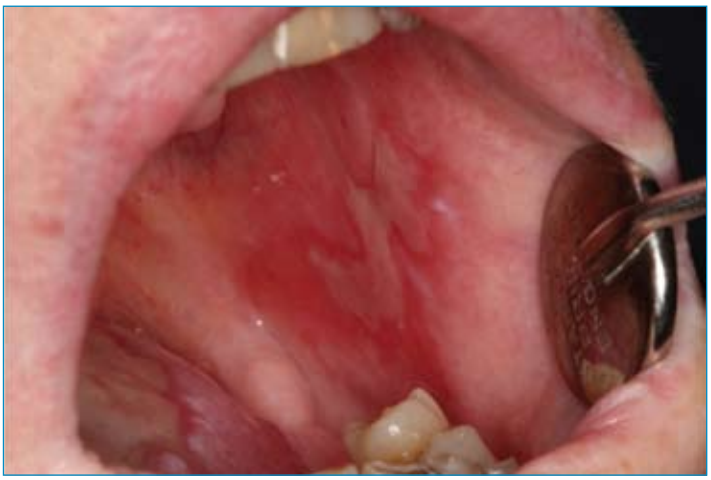

Figure 1: The left buccal mucosa demonstrating an ulcer, surrounded by erythema and faint white striations.

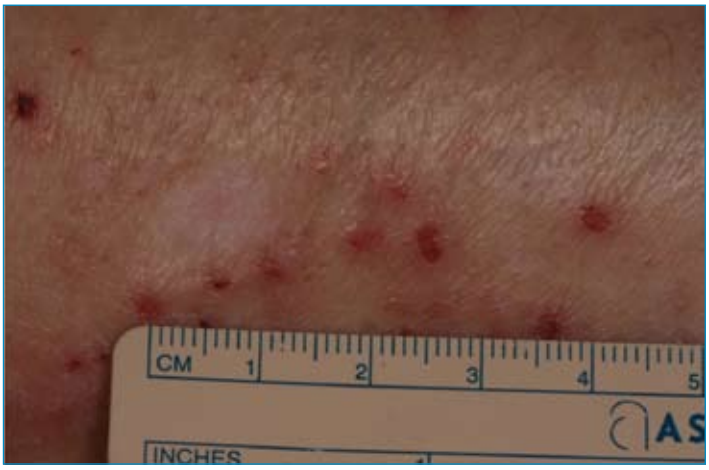

Figure 2: Erythematous ulcers on the extensor surfaces of the lower extremities.

Intra-oral examination revealed large ulcers on the buccal mucosae, floor of mouth and tongue. The lesions were surrounded by a broad band of erythema with white striations (Figure 1).

Further examination revealed that the patient was emaciated, with ulcers and crusting on her lower back and on the extensor surfaces of the extremities (Figure 2). An ulcer was noted on the ventrolateral surface of the right foot.

A clinical differential diagnosis of vesiculo-ulcerative conditions including erosive OLP was made.

An incisional biopsy of the lesion of the left buccal mucosa was done, and an excisional biopsy of one of the lesions on the extensor surface of the left leg. Biopsy specimens were preserved

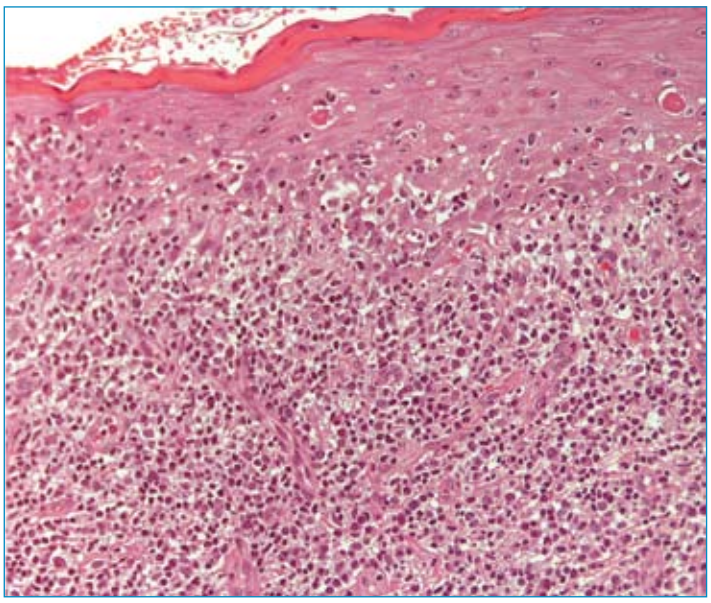

Figure 3: Photomicrograph of the H&E stained specimen of the buccal mucosa.

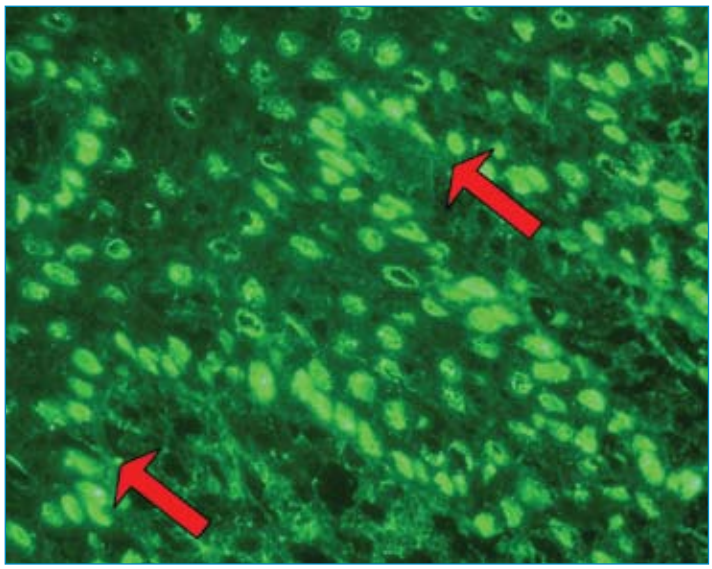

Figure 4: Photomicrograph of fluorescent anti-IgG antibodies directed against the nuclei of basal keratinocytes.

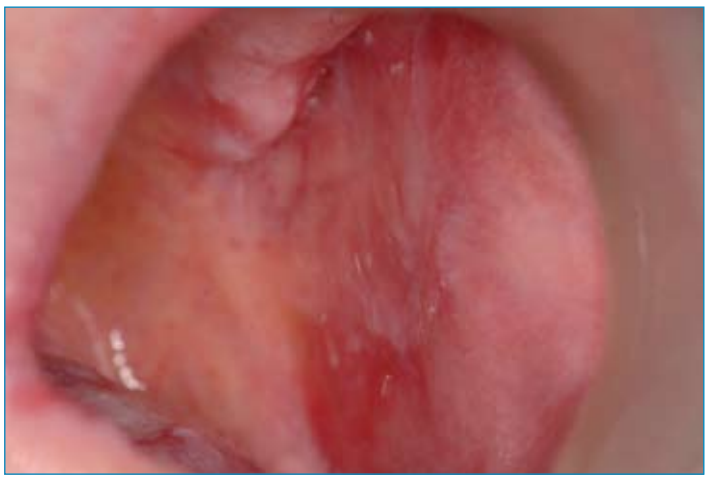

Figure 5: Left buccal mucosa demonstrating significant resolution of the ulcer but with residual erythema.

in 10% buffered formalin for haematoxylin and eosin (H&E) staining and histological examination and a fresh sample was submitted for direct immunofluorescence (DIF) analysis. A blood sample was also submitted for indirect immunofluorescence (IIF). Immunofluorescence is used to distinguish between immune mediated vesiculo-ulcerative conditions.[3]

Microscopical examination of the H&E stained specimen of the oral mucosa showed an ulcer surrounded by stratified squamous epithelium with focal hyperkeratosis. A diffuse, mixed sub-epithelial inflammatory cell infiltrate consisting of lymphocytes, plasma cells, mast cells and histiocytes was present extending into the underlying connective tissue (Figure 3).

DIF revealed the presence of prominent IgG staining directed against the nuclei of the stratified squamous epithelial cells, more prominent in the basal layers (Figure 4). A similar pattern of positivity was seen with IgA staining.

The blood sample submitted for IIF did not demonstrate IgG adherence.

Histological examination of the skin showed a mild sub-epithelial inflammatory cell infiltrate, predominantly of lymphocytes and histiocytes. DIF demonstrated peri-nuclear IgG and IgA deposits in the cells of the basal layer of the epidermis, similar to the oral mucosal specimen.

Based on the DIF results a diagnosis of CUS with concurrent skin involvement was made. Because hydroxychloroquine is not available in South Africa, the patient was given 200mg of chloroquine per day, and after three months there had been significant improvement, particularly in the oral mucosal lesions (Figure 5).

The patient was then referred to the Dermatology Clinic at Steve Biko Academic Hospital (Pretoria) for further management of the skin lesions. A biopsy of the ulcer on her right foot was performed because that lesion had not responded to the treatment with chloroquine. A similar DIF picture was seen as in the intra-oral biopsies. Ciclosporin (200mg/day) was prescribed for treatment of the skin lesions. After six months of this treatment, the ulcer on her right foot was significantly better.

DISCUSSION

Incidence and prevalence

The English literature describes 39 cases, 35 women and 4 men, with most cases occurring between 40 and 60 years of age.[2]

Aetiology and pathogenesis

CUS is an immune-mediated disease in which antinuclear antibodies are directed against the chronic ulcerative stomatitis protein (CUSP - ΔNp63α).[4,5] Lee *et al* (1999) described the genetic changes of CUS in detail. They postulated that CUSP acts by down-regulating the apoptosis-inducing effects of p53. As CUSP is an anti-apoptotic protein, inhibition of the action of CUSP by auto-antibody binding may lead to apoptotic epithelial injury through the p53 pathway.[4] This may be especially significant in the oral cavity, where epithelial turnover is high and minor trauma is common.[5]

Clinical presentation and features

Oral lesions of CUS are characterised by erythematous macules, large tender erosions, ulcers and vesicles. Lesions may occur on keratinised and on non-keratinised mucosa. Pain is a common feature of these lesions. Patients may also suffer from weight loss, insomnia, malaise, depression, apathy, a feeling of helplessness, nervousness, fatigue and discomfort on eating and drinking.[2] Lesions generally heal without scarring.[6] The erosive lesions of

CUS can be mistaken for erosive lesions of OLP, with patients experiencing periods of exacerbation and remission.[6] The cases reported by Islam *et al* (2007) showed ulcers surrounded by fine white striae.[2]

Histological features

CUS as seen on H&E stained histological specimens is non-specific.[7] The potential for confusion of CUS with OLP warrants the use of DIF.

With DIF, IgG antibodies in CUS are found bound to nuclei of keratinocytes of the basal and suprabasal epithelial cell layers. This IgG staining shows a unique stratified epithelial specific-antinuclear antibody (SES-ANA) pattern.[1,8] The SES-ANA pattern has a speckled or finely granular appearance usually in a peri-nuclear distribution.[2] The same SES-ANA pattern may also be seen in the unaffected skin of CUS patients.[2,9] Antinuclear antibodies are also seen in keratinocytes in systemic lupus erythematosus (SLE), in CREST syndrome and in mixed connective tissue disease, but are then located higher up in the stratum spinosum.[7]

When taking biopsies for DIF, fresh specimens should either be taken to the laboratory for immediate processing; or they should be transported without delay in Michel's transport medium. The specimen should include adequate peri-lesional mucosa because areas of ulceration are devoid of epithelium. The biopsy incision should not be made at an angle to the surface, since visualisation of the full thickness of epithelial layers is necessary.[7]

Although IIF will confirm the diagnosis, monkey or guinea pig oesophagus should be used as the substrate instead of mouse kidney or Hep2 cells, because they show higher antibody titres.[6] However these substrates are not freely available. When enzyme linked immunosorbent assay (ELISA) testing for CUS becomes commercially available it may prove useful in evaluating the prognostic value of antibody titres and allow correlation with treatment responses.[10]

Diagnosis

Chorzelski, one of the first authors to describe CUS in 1990,[8] proposed major and minor diagnostic criteria to facilitate diagnosis. The major criterion for diagnosis of CUS is the presence of erosive oral lesions with the characteristic SES-ANA pattern on using DIF. To further substantiate diagnosis of CUS, minor criteria are the chronic course with relapses, greater likelihood of the patient's being female, older age, and a good response to treatment with hydroxychloroquine or hydroxychloroquine (chloroquine) combined with corticosteroid.[9] ELISA may become the diagnostic test of choice in future since a recent experimental study has demonstrated excellent sensitivity and specificity.[10]

The differential diagnosis of CUS should include OLP, lichenoid stomatitis, pemphigus vulgaris, bullous pemphigoid, mucous membrane pemphigoid, linear IgA disease, dermatitis herpetiformis, epidermolysis bullosa acquisita and SLE.[2]

Treatment

The use of glucocorticoids in the treatment of CUS may be disappointing but may provide some symptomatic relief and clinical improvement. The treatment of choice is hydroxychloroquine which may bring about remission in up to 70 % of patients.[2] Therapeutic doses of 200mg hydroxychloroquine (or chloroquine if hydroxychloroquine is unavailable) per day are recommended. [2,6,9]

This drug acts by interfering with the antigen-processing mechanism of macrophages and other antigen presenting cells. Reduced antigen presentation down-regulates the immune response leading to improvement of the immune-mediated lesions.[11]

Important side effects of treatment with hydroxychloroquine include irreversible retinopathy, toxic psychosis, neuromyopathy, agranulocytosis and aplastic anaemia.[6] Owing to hydroxychloroquine's ocular toxicity, the American Academy of Ophthalmology has issued recommendations on screening, which is best done by an ophthalmologist.[12]

Topical corticosteroids may be added to the treatment regime, effectively lowering the dose of hydroxychloroquine required and therefore limiting possible side effects.[9]

Skin involvement is rare, therefore if found, double pathology should be considered.

CONCLUSIONS

Chronic ulcerative stomatitis is a distinct clinical entity. Its clinical similarities to other vesiculo-ulcerative conditions, in particular erosive OLP, and its non-specific histological features require the use of DIF and IIF.

A correct diagnosis is essential since CUS is resistant to immune-modulating drugs such as glucocorticoids; but responds favourably to chloroquine (hydroxychloroquine). Although ciclosporin was of great value for treatment of the skin lesions in this case, with our limited experience, we cannot recommend it as monotherapy in the treatment of CUS.

Declaration: No conflict of interest.

REFERENCES

1. Jaremko WM, Beutner EH, Kumar V, Kipping H, Condry P, Zeid MY, *et al*. Chronic ulcerative stomatitis associated with a specific immunologic marker. *J.Am.Acad.Dermatol* 1990; **22**:215-220.
2. Islam MN, Cohen DM, Ojha J, Stewart CM, Katz J, Bhattacharyya I. Chronic ulcerative stomatitis: diagnostic and management challenges--four new cases and review of literature. *Oral Surg.Oral Med.Oral Pathol.Oral Radiol.Endod* 2007; **104**:194-203.
3. Rinaggio J, Crossland DM, Zeid MY. A determination of the range of oral conditions submitted for microscopic and direct immunofluorescence analysis. *J.Periodontol* 2007; **78**:1904-1910.
4. Lee LA, Walsh P, Prater CA, Su LJ, Marchbank A, Egbert TB, *et al*. Characterization of an autoantigen associated with chronic ulcerative stomatitis: the CUSP autoantigen is a member of the p53 family. *J.Invest.Dermatol* 1999; **113**:146-151.
5. Solomon LW, Neiders ME, Zwick MG, Kirkwood KL, Kumar V. Autoimmunity to deltaNp63alpha in chronic ulcerative stomatitis. *J.Dent.Res* 2007; **86**:826-831.
6. Solomon LW, Aguirre A, Neiders M, Costales-Spindler A, Jividen GJ,Jr, Zwick MG, *et al*. Chronic ulcerative stomatitis: clinical, histopathologic, and immunopathologic findings. *Oral Surg.Oral Med.Oral Pathol.Oral Radiol. Endod* 2003; **96**:718-726.
7. Solomon LW. Chronic ulcerative stomatitis. *Oral Dis* 2008; **14**:383-389.
8. Chorzelski TP. Chronic ulcerative stomatitis (CUS): a new disease entity with specific immunological marker (SES-ANA). *Przegl.Dermatol* 1990; **77**:229-232.
9. Chorzelski TP, Olszewska M, Jarzabek-Chorzelska M, Jablonska S. Is chronic ulcerative stomatitis an entity? Clinical and immunological findings in 18 cases. *Eur.J.Dermatol* 1998; **8**:261-265.
10. Solomon LW, Stark PC, Winter L, Kumar V, Sinha S. ELISA test for p63 antibodies in chronic ulcerative stomatitis. *Oral Dis* 2010; **16**:151-155.
11. Fox RI. Mechanism of action of hydroxychloroquine as an antirheumatic drug. *Seminars in Arthritis and Rheumatism* 1993; **23**:82-91.
12. Angi M, Romano V, Valldeperas X, Romano F, Romano MR. Macular sensitivity changes for detection of chloroquine toxicity in asymptomatic patient. *Int Opthalmol* 2010; **30**:195-197.

EOUS06042011