ECRONICON OPEN ACCESS

EC DENTAL SCIENCE
Commentary

The Protracted Pustule-Chronic Ulcerative Stomatitis

Anubha Bajaj*

Department of Histopathology, Panjab University, A.B. Diagnostics, India

***Corresponding Author:** Anubha Bajaj, Department of Histopathology, Panjab University, A.B. Diagnostics, India.

Received: June 01, 2022; **Published:** June 28, 2022

Preface

Chronic ulcerative stomatitis is designated as an exceptional, chronic ulcerative disorder incriminating the oral cavity. The condition was initially described by Parodi., *et al*. and Jaremko., *et al*. in 1990 [1,2].

Chronic ulcerative stomatitis simulates cutaneous, lichen planus-like lesions or oral lichen planus (OLP) on clinical and histological grounds. Also, chronic ulcerative stomatitis can manifest as non-specific or lichenoid mucositis, akin to oral lichen planus (OLP). The terminology of erosion-ulceration may be conveniently adopted to describe the lesions.

Typically, chronic ulcerative stomatitis exhibits chronic oral erosions and ulcers which may occasionally be circumscribed by white striae. Specific, diagnostic antinuclear antibodies (ANA) designated as stratified epithelium-specific antinuclear antibodies (SES-ANA) may be discerned through direct immunofluorescence (DIF) within oral mucosa or cutaneous lesions or within serum with indirect immunofluorescence (IIF).

Also, minimal response to corticosteroid therapy, adequate response to antimalarial agents and frequent association with lichen planus-like cutaneous lesions are characteristic.

Appropriate disease discernment may frequently and significantly be delayed. Chronic, recalcitrant, steroid-unresponsive oral mucosal erosion or ulceration may be subjected to immunofluorescence in order to detect possible emergence of chronic ulcerative stomatitis. Chronic ulcerative stomatitis as a condition may be frequently misinterpreted and underdiagnosed.

Disease pathogenesis

Epithelial antigen incriminated in the pathogenesis of chronic ulcerative stomatitis is postulated to be a multi-molecular, non-histonic deoxy ribonucleic acid (DNA) protein complex which engenders circulating antibodies against a mammalian epithelial antigen on account of enzymes which denature DNA and hydrolyse proteins [3,4].

The principal autoantigen of chronic ulcerative stomatitis is an epithelial nuclear protein of 70 kilo-dalton molecular weight, designated as "chronic ulcerative stomatitis protein" (CUSP) and engenders antibodies binding to epithelial cell nuclei [3,4].

Chronic ulcerative stomatitis protein (CUSP) emerges as an isoform of p63 protein designated as "ΔNp63α". The p63 gene is situated upon chromosome 3q27-29 and encodes six p53-homologous proteins. Protein ΔNp63α is predominantly epithelial and emerges as a crucial contributory factor in the development of oral epithelium and cutis.

Antibodies associated with chronic ulcerative stomatitis are directed towards ΔNp63α [3,4].

In addition to IgG, around 52% instances depict circulating IgA antibodies and incriminated subjects may demonstrate identical clinical manifestations. Also, immune-dominant regions of protein ΔNp63α occur as N-terminal and DNA-binding domains whereas antibody cross-reactivity with p53-, p63 and p73 isoforms appears restricted [3,4].

The exceptional, immune-mediated, muco-cutaneous disorder is posited to emerge on account of immunoglobulin IgG binding to nuclear protein ΔNp63α within the basal and para-basal layers of stratified squamous epithelium. Aforesaid interaction engenders detachment of adjacent keratinocytes and cellular separation from basement membrane [3,4].

Chronic ulcerative stomatitis may be contemplated as a variant of oral lichen planus (OLP) wherein ΔNp63α configured autoimmune lesions exemplify additional immunological and pathogenic mechanisms with epithelial cell denaturation, features which may indicate a lichen planus variant [3,4].

Pathogenic SES-ANA engenders epithelial detachment with incrimination of epithelial nuclei of basal keratinocytes. Aforesaid manifestation may be obtained by adding monoclonal ΔNp63α autoantibody to cutaneous surfaces or human skin equivalent (HSE).

The autoimmune chronic ulcerative stomatitis exhibits chiefly IgG autoantibodies (SES-ANA) which bind to speckled nuclear protein ΔNp63α (CUSP) situated upon basal and para-basal layers of stratified squamous epithelium. The protein initiates a separation of keratinocytes from basal membrane and enhances intracellular segregation with consequent emergence of the characteristic ulcer of chronic ulcerative stomatitis [5,6].

The stratified epithelium-specific antinuclear antibody (SES-ANA) may also be discerned in autoimmune disorders such as systemic lupus erythematosus (SLE), scleroderma, mixed connective tissue disease or CREST syndrome with Calcinosis cutis, Raynaud phenomenon, Oesophageal dysfunction, Sclerodactyly and Telangiectasia (CREST) syndrome. Antibody deposition is observed through entire thickness of the epithelium [5,6].

A female predominance is observed with a female to male ratio of nearly ~14:1. The condition may occur within the third decade to eighth decade with a mean age of disease emergence at 61 years. A racial predilection is observed with majority (~90%) instances occurring within the Caucasian population [5,6].

Clinical elucidation

Majority of incriminated subjects exhibit oral discomfort, pain, soreness, tenderness, burning or stinging sensation and dysphagia. Common clinical representation emerges as erythema, pain, burning sensation, leukoplakia, mucosal ulceration or erosion. Oral cavity lesions can manifest as non healing ulcers or erosions along with or in the absence of desquamative gingivitis [5,6].

The ulcers are circumscribed by an erythematous zone with streaky keratosis, akin to lesions of erosive oral lichen planus [5,6].

Frequently, chronic ulcerative stomatitis exemplifies as a white lesion, erythema, mucosal erosion and ulceration. Appropriate distinction between oral erosion, ulceration or erythema may be challenging [6,7].

Mucosal ulceration and erosions may be associated with white lesions, especially Wickham's striae-like lesions. Also, erosion- ulceration pattern with circumscribing white striae is frequently observed.

Additionally, features such as desquamation, xerostomia, vesicle formation and gingival Nikolsky's sign may be delineated. Consequently, clinical differentiation from autoimmune bullous diseases may be challenging [6,7].

Chronic ulcerative stomatitis exhibits characteristic clinical features as mucosal erosion and ulceration, in contrast to white striae observed in oral lichen planus [6,7].

Oral mucosal lesions are frequently situated within the buccal mucosa or gingiva. Additionally, widespread oral mucosal involvement is accompanied by lesions upon the tongue, hard palate or labial mucosa. Extra-oral cutaneous and mucosal lesions may represent as lichen planus or lichen planus- like lesions. Extra-oral lesions predominantly incriminate cutaneous surfaces, nails, hair or mucous membranes as the conjunctiva [6,7].

Oral mucosal lesions represent lichenoid features, emerge as oral lichen planus or exhibit non-specific inflammation designated as "non-specific mucositis" [6,7].

Histological elucidation

Upon morphological assessment, chronic ulcerative stomatitis is accompanied by a characteristic, mixed inflammatory infiltrate composed of significant quantities of mature lymphocytes and plasma cells. Superimposed stratified squamous epithelium is atrophic. Subepithelial tissue appears separated from subjacent connective tissue stroma [7,8].

Chronic ulcerative stomatitis may manifest histological features of oral lichen planus as a parakeratotic or atrophic stratified squamous epithelium, vacuolar degeneration of basal epithelial cells, cytoid bodies, band-like chronic inflammatory infiltrate confined to the dermo-epidermal interface and saw-toothed rete ridges [7,8].

Nevertheless, the sharply defined, band-like inflammatory infiltrate of oral lichen planus appears contained within the superficial lamina propria, in contrast to lesions of chronic ulcerative stomatitis. Typically, the stratified squamous epithelium is atrophic and inflammatory infiltrate is comprised of significant quantities of plasma cells and small lymphocytes. Thus, the inflammatory infiltrate is an admixture of T lymphocytes and plasma cells [7,8].

Differential diagnosis

The exceptional chronic ulcerative stomatitis requires a segregation from lesions of lichen planus (LP), pemphigus vulgaris, cicatricial pemphigoid, lichenoid mucositis, erosive oral lichen planus, reticular oral lichen planus, vesiculo-bullous diseases as benign mucous membrane pemphigoid or pemphigus, systemic lupus erythematous (SLE) or erythema multiforme [8,9].

Also, distinction is required from clinically identical, diffuse, chronic ulcerative mucosal conditions such as oral lichen planus (OLP), pemphigus vulgaris, cicatricial pemphigoid or bullous lupus erythematosus [8,9].

Lichenoid mucositis is associated with deposition of fibrinogen within the basement membrane zone [9,10].

Investigative assay

Direct immunofluorescence (DIF) of lesions of chronic ulcerative stomatitis typically exhibits the IgG-ΔNp63α interaction with speckled stratified epithelium-specific antinuclear antibodies (SES-ANA) confined to inferior third of the epithelium. Occasionally, lesions may display shaggy fibrinogen deposited along the basement membrane [9,10].

Chronic ulcerative stomatitis can be appropriately diagnosed by direct immunofluorescence (DIF) which depicts the characteristic SES-ANA IgG speckled pattern confined to keratinocyte nuclei of basal and parabasal layer of lower third of stratified squamous epithelium.

Also, fibrinogen deposition along the basement membrane with frequent extension into superficial lamina propria may be exemplified, features which are designated as a "shaggy appearance" [9,10].

Direct immunofluorescence can be employed for discerning deposition of IgA, IgM, fibrinogen and C3 [9,10].

In the absence of availability of direct immunofluorescence (DIF), an indirect immunofluorescence (IIF) is the ideal investigation to appropriately discern chronic ulcerative stomatitis [9,10].

Therapeutic options

Chronic ulcerative stomatitis depicts an inadequate therapeutic response to corticosteroids whereas response to antimalarial agents is superior. Thus, secondary antimalarial therapy may be beneficial in a majority (~90%) instances whereas combination therapy is comprehensively (100%) efficacious. However, the antimalarial agent hydroxychloroquine is associated with side effects such as gastrointestinal symptoms, agranulocytosis, aplastic anaemia, toxic psychosis, neuromyopathy or irreversible retinopathy [10,11].

Additionally, combination treatment regimens as tacrolimus and cyclosporine may be curative. Mild disease may be controlled with antimalarial agents and relapses during tapered therapy may arise infrequently [10,11].

Reoccurring lesions may be subjected to repetitive therapy [10,11].

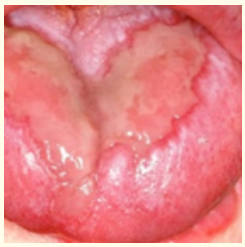

Figure 1: *Chronic ulcerative stomatitis exhibiting ulceration of tongue with an erythematous margin [12].*

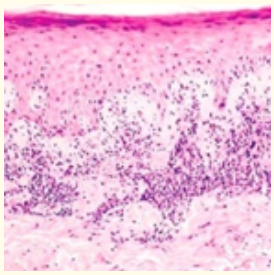

Figure 2: *Chronic ulcerative stomatitis exemplifying an ulcerated oral mucosa with layered atrophic stratified squamous epithelium and an inflammatory exudate composed of lymphocytes and plasma cells [12].*

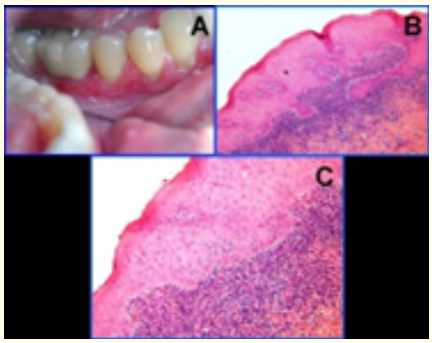

Figure 3: *Chronic ulcerative stomatitis enunciating a gingival ulcer layered by atrophic stratified squamous epithelium with a subjacent chronic inflammatory infiltrate of lymphocytes and plasma cells [13].*

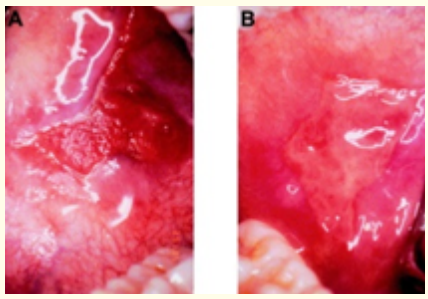

Figure 4: *Chronic ulcerative stomatitis depicting ulceration of oral buccal mucosa with erythema and whitish zones [14].*

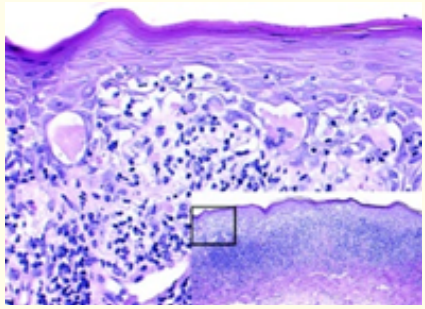

Figure 5: *Chronic ulcerative stomatitis displaying an atrophic stratified squamous epithelium superimposed upon an inflammatory exudate of lymphocytes and plasma cells [14].*

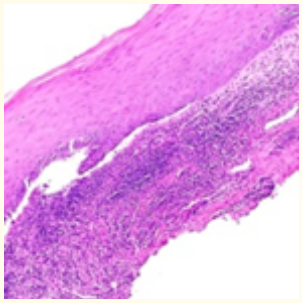

Figure 6: *Chronic ulcerative stomatitis demonstrating atrophic stratified squamous epithelium with a subjacent chronic inflammation of plasma cells and lymphocytes invading the ulcerated zone [15].*

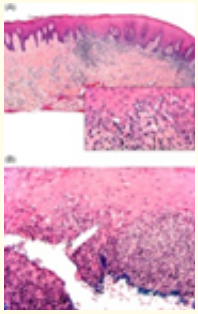

Figure 7: *Chronic ulcerative stomatitis delineating an atrophic lining epithelium covering an inflammatory exudate of lymphocytes and plasma cells [16].*

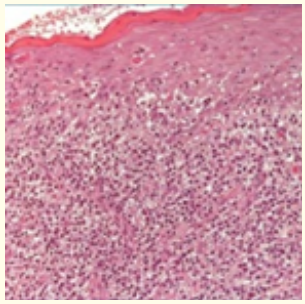

Figure 8: *Chronic ulcerative stomatitis exhibiting an atrophic lining epidermal layer superimposed upon a chronic inflammatory exudate of lymphocytes and macrophages [17].*

Bibliography

1. Parodi A and Cardo PP. "Patients with erosive lichen planus may have antibodies directed to a nuclear antigen of epithelial cells: a study on the antigen nature". *Journal of Investigative Dermatology* 94.5 (1990): 689-693.

2. Jaremko WM., *et al*. "Chronic ulcerative stomatitis associated with a specific immunologic marker". *Journal of the American Academy of Dermatology* 22.2-1 (1990): 215-220.

3. Herzum A., *et al*. "The 30th birthday of chronic ulcerative stomatitis: A systematic review". *International Journal of Immunopathology and Pharmacology* 35 (2021): 20587384211052437.

4. Reddy R., *et al*. "Seventeen New Cases of Chronic Ulcerative Stomatitis with Literature Review". *Head and Neck Pathology* 13.3 (2019): 386-396.

5. Stoopler ET., *et al*. "Novel combination therapy of hydroxychloroquine and topical tacrolimus for chronic ulcerative stomatitis". *International Journal of Dermatology* 60.4 (2021): e162-e163.

6. Jacyk WK., *et al*. "Chronic ulcerative stomatitis and lichen planus: just a coincidence or a direct link between the two diseases?" *Dermatologia Kliniczna* 14.3 (2012): 127-129.

7. Qari H., *et al*. "The diagnostic challenges of separating chronic ulcerative stomatitis from oral lichen planus". *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology* 120.5 (2015): 622-627.

8. Alshagroud R., *et al*. "Clinicopathologic significance of in vivo antinuclear autoantibodies in oral mucosal biopsies". *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology* 124.5 (2017): 475-482.

9. Ko EM., *et al*. "Chronic ulcerative stomatitis: case series of an under-recognized entity". *Journal of Cutaneous Pathology* 45.12 (2018): 927-932.

10. Azzi L., *et al*. "Chronic ulcerative stomatitis: a comprehensive review and proposal for diagnostic criteria". *Oral Diseases* 25.6 (2019): 1465-1491.

11. Ferrisse T., *et al*. "Chronic ulcerative stomatitis: A systematic review of the clinical and microscopic features". *Medicina Oral Patología Oral y Cirugia Bucal* 24.6 (2019): 1.

12. Image 1 and 2 Courtesy: Semantic scholar.

13. Image 3 Courtesy: Science direct.

14. Image 4 and 5 Courtesy: OOOOjournal.net.

15. Image 6 Courtesy: Gipatec.com.

16. Image 7 Courtesy: Wiley online library.

17. Image 8 Courtesy: Research gate.

Volume 21 Issue 7 July 2022