Head and Neck Pathology (2019) 13:386–396
https://doi.org/10.1007/s12105-018-0982-7

ORIGINAL PAPER

Seventeen New Cases of Chronic Ulcerative Stomatitis with Literature Review

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Received: 30 July 2018 / Accepted: 26 October 2018 / Published online: 29 October 2018

Abstract

Chronic ulcerative stomatitis (CUS) is a poorly understood disease with clinical and histologic overlap with lichen planus (LP). Unlike classic LP, direct immunofluorescence (DIF) studies in cases of CUS exhibit a granular pattern of IgG in nuclei of basal and parabasal cells. This study assesses the demographic, clinical, histologic, and DIF features of CUS. It is important to differentiate CUS from LP and other vesiculobullous diseases (VBD) because lesions of CUS are resistant to steroid therapy, which is typically used to control LP and VBD. A literature review and IRB-approved retrospective search of CUS was performed within the archives of the University of Florida (UF) Oral Pathology Biopsy Service from 2007 to 2017. Fifty-two cases were identified from the literature and seventeen new cases were identified in our series. All UF patients were female and the median age was 64-years. The majority of patients were Caucasian and the most common location was buccal mucosa. Frequent clinical presentations were pain, erythema, leukoplakia, and ulcerations. Histologic features included epithelial separation, atrophic epithelium, and a chronic inflammatory infiltrate. All cases were confirmed with DIF testing that showed a speckled pattern of IgG staining in basal and parabasal cell nuclei. Fibrinogen was present in eleven cases and two cases were positive for C3. The results of our series are in accordance with the literature. Since CUS has overlapping features with LP and VBD, clinicians and pathologists should consider this entity and confirm diagnosis with DIF testing when recalcitrant oral ulcerative diseases are encountered.

Keywords Chronic ulcerative stomatitis · Histology · Oral pathology · Direct immunofluorescence antibody technique

Introduction

Chronic ulcerative stomatitis (CUS) is a rare, immune-mediated mucocutaneous disorder that was first reported by Jaremco et al. in 1990 [1]. The proposed etiopathogenesis is the binding of immunoglobulin IgG to the nuclear protein ΔNp63α in the basal and parabasal layers of stratified squamous epithelium [2–11]. This interaction results in the detachment of keratinocytes from one another and from the basement membrane [2, 12]. Direct immunofluorescence (DIF) studies reflect this IgG-ΔNp63α interaction, as cases of CUS have a speckled pattern of IgG in the nuclei of the basal and parabasal cell layers of the epithelium [1–5]. This pattern, known as stratified epithelial specific antinuclear antibody (SES-ANA), is also found in systemic lupus erythematosus (SLE); scleroderma; Calcinosis cutis, Raynaud phenomenon, Esophageal dysfunction, Sclerodactyly and Telangiectasia (CREST) syndrome; and mixed connective tissue disease [13]. In CUS this pattern is confined to the basal and parabasal cell layers while in other connective tissue diseases it is positive throughout the thickness of the epithelium [14].

The histopathologic features of CUS are similar to oral lichen planus (OLP), however typically the epithelium is more atrophic and the inflammatory infiltrate includes a significant number of plasma cells in addition to lymphocytes [3–7, 14]. In the oral cavity, CUS manifests clinically as non-healing ulcerative or erosive lesions with or without desquamative gingivitis [2, 5, 7, 9, 12]. The ulcers are surrounded by zones of erythema and streaky keratosis that

This study was presented as an oral presentation at the Joint IAOP and AAOMP Meeting in Vancouver, BC, Canada, June 2018.

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resemble erosive OLP [2, 3, 6, 7, 14, 15]. This study will assess the demographic, clinical, histologic, and DIF features of CUS to further define this rare entity.

Materials and Methods

A literature review was performed on all published cases of CUS. Additionally, an IRB-approved retrospective search was performed within the archives of the University of Florida (UF) Oral Pathology Biopsy Service between the years 2007 and 2017 for cases diagnosed as CUS. A search was done by diagnosis code for CUS to identify cases. Materials accessed included the history sheets, biopsy reports, and slides. Exclusion criteria included cases with inconclusive diagnosis, cases without DIF testing for confirmation, and cases with missing clinical data or slide material. A database was created that included the patient's age, gender, race, location, clinical appearance, clinical impression, symptoms, duration, results of DIF testing, and diagnosis. Due to the nature of the case series and literature review, the data was analyzed qualitatively.

Results

Fifty-two cases of CUS were identified from the literature [1, 3, 7, 8, 14–22] and seventeen cases were retrieved from the UF Oral Pathology Biopsy Service archives (Table 1). The median age in our series was 64-years (range 47–83 years) while the median age in the literature was 59-years (range 22–86 years). All patients in our series were female, while in the literature 90% of patients were female and 10% of patients were male. The majority of our patients (65%) and in literature (50%) were Caucasian (Table 2).

Buccal mucosa was the most common location in our series (53%) and the literature (37%). Gingiva was the second most common location in our series (47%), but the third most common location in the literature (27%). The second most common location historically was the tongue (31%) (Table 3).

The clinical impression was OLP in fifteen of our seventeen cases. Of these fifteen cases, fourteen cases were erosive OLP and one case was reticular OLP. Three cases included vesiculobullous diseases (pemphigoid, pemphigus, or both) as a differential and one case listed SLE as a differential. Erythema multiforme (EM) was the clinical impression in one case. One case did not provide a clinical impression.

The most common clinical presentations in our series were erythema (76%) (Fig. 1a, b) and pain/burning (76%), leukoplakia (65%) (Fig. 1c), and ulcerations/erosions (35%) (Fig. 1d). In the literature, the most common clinical presentations were the same, but in differing order. They were ulcerations/erosions (65%), leukoplakia (40%), erythema (37%), and pain/burning (29%) (Table 4).

Histologic features for the cases in our series included sub-epithelial separation from the underlying connective tissue (Fig. 2a), atrophic epithelium (Fig. 2b), and an inflammatory infiltrate that contained a significant number of plasma cells and lymphocytes (Fig. 2c, d). All cases in our series were confirmed with DIF testing that showed a characteristic speckled pattern of IgG in the nuclei of basal and parabasal cells (Fig. 3a). Fibrinogen was also present in eleven of these cases (Fig. 3b) and two cases were faintly positive for C3. None of the cases in our series were positive for IgA or IgM. A summary of DIF results for our case series and the literature review is demonstrated in Fig. 4.

Discussion

The results for age, gender, race, location, clinical presentation, histologic features, and DIF in our case series are similar to what exists in the literature. Our case series and the literature demonstrate that CUS occurs in older females. Although the majority of cases occurred in Caucasians, 24% of the cases in our series and 46% of the cases in the literature did not specify race.

Also of note is that none of the lesions in our current series occurred on the tongue whereas the tongue was the second most common location in the literature. CUS is known to present in many mucosal locations. It is probable that clinicians in our series chose sites that were easier to biopsy, such as the buccal mucosa and gingiva, and failed to report that lesions were also present on the tongue.

The clinical impression in most of our cases was OLP. It is possible that the clinicians did not suspect CUS because they may lack awareness of it. However, it must be noted that striae, the characteristic feature of reticular OLP, was not one of the major clinical presentations either in our study (12%) or in the literature (13%). The most common clinical presentations were ulcerations/erosions, erythema, leukoplakia, and pain/burning. These clinical features overlap with erosive OLP and autoimmune diseases, including benign mucous membrane pemphigoid, pemphigus vulgaris, and SLE. Our study had 5 cases that reported blisters/positive Nikolsky sign. Although rare, cases of CUS that produce blisters/positive Nikolsky sign have been reported [16, 18]. None of our cases had skin lesions or ocular involvement, but 25% of the cases in the literature had concurrent skin lesions and 1 case [20] reported conjunctivitis and ectropion.

DIF studies of lesional and perilesional oral mucosa specimens revealed a speckled, finely granular pattern of IgG deposition in the nuclei of keratinocytes. All but one case [16] of CUS presented with this SES-ANA pattern.

Table 1 Summary of results from the literature review and current case series

Reference	Age	Gender	Race	Location	Clinical presentation	DIF results
Jaremko et al. [1]	59	Female	African-American	Buccal mucosa, gingiva	Painful erosions, desquamative gingivitis, white reticular lesions, skin lesions	Nuclear: speckled pattern of IgG and IgA DEJ: Fibrinogen
	77	Female	Caucasian	Buccal mucosa, tongue	Soreness and erosions	Nuclear: speckled pattern of IgG and IgA DEJ: Fibrinogen
	81	Female	Caucasian	Buccal mucosa, tongue, hard palate	Pain, erythema, erosions, skin lesions	Nuclear: speckled pattern of IgG DEJ: Fibrinogen
	77	Female	Caucasian	Gingiva, upper labial mucosa	Painful ulcerations	Nuclear: speckled pattern of IgG DEJ: Fibrinogen
Parodi et al. [8]	64	Female	Unknown	Buccal mucosa, lower labial mucosa	Erosive lesions, skin lesions	Nuclear: speckled pattern of IgG DEJ: Granular IgM
	53	Female	Unknown	Buccal mucosa, lower labial mucosa	Erosive lesions, skin lesions	Nuclear: speckled pattern of IgG DEJ: Fibrinogen
Beutner et al. [18]	59	Female	Caucasian	Gingiva	Erosions of the oral mucosa	Speckled pattern of IgG
	64	Female	Caucasian	Buccal mucosa, tongue	Erosions of the oral mucosa	Speckled pattern of IgG
	45	Female	Caucasian	Buccal mucosa, tongue	Severe erosions	Speckled IgG deposits in epithelial nuclei
	48	Male	Caucasian	Gingiva, tongue	Erythema and positive Nikolsky sign. Clinical impression: erosive LP or cicatricial pemphigoid	Speckled IgG deposits in epithelial nuclei
Church et al. [17]	71	Female	Caucasian	Gingiva	Painful, burning mouth. Moderate to severe erosive lesions. Clinical impression: erosive LP	Speckled pattern of IgG, shaggy Fibrinogen at the BMZ
Lewis et al. [19]	73	Female	Caucasian	Buccal mucosa, tongue	Erosive stomatitis, skin lesions	Nuclear deposits of IgG with a speckled pattern, Fibrinogen deposits in a lichenoid pattern at the DEJ
Worle et al. [16]	40	Female	Caucasian	Gingiva, hard palate, tongue	Painful blisters, erosions, and ulcerations	Negative DIF

Table 1 (continued)

Reference	Age	Gender	Race	Location	Clinical presentation	DIF results
Chorzelski et al. [20]	51	Female	Unknown	Tongue, labial mucosa	Erosions	Speckled pattern of IgG
	63	Female	Unknown	Widespread involvement	Erosions, ulcerations, and LP-like white lesions	DIF not performed, diagnosis confirmed with IIF
	68	Female	Unknown	Widespread involvement	Erosions, ulcerations	DIF not performed, diagnosis confirmed with IIF
	56	Female	Unknown	Tongue, labial mucosa	Erosions	Speckled pattern of IgG
	66	Female	Unknown	Tongue, lower labial mucosa	Erosions	DIF not performed, diagnosis confirmed with IIF
	46	Female	Unknown	Widespread involvement	Erosions, skin lesions	DIF not performed, diagnosis confirmed with IIF
	84	Female	Unknown	Widespread involvement	Erosions, conjunctivitis/ectropion	Speckled pattern of IgG
	35	Female	Unknown	Widespread involvement	Erosions, LP changes, skin lesions	DIF not performed, diagnosis confirmed with IIF
	75	Female	Unknown	Tongue, labial mucosa	Erosions	Speckled pattern of IgG
	86	Female	Unknown	Widespread involvement	Erosions, ulcerations, white mucosa, skin lesions	DIF not performed, diagnosis confirmed with IIF
	66	Female	Unknown	Widespread involvement	Erosions, ulcerations	DIF not performed, diagnosis confirmed with IIF
	48	Male	Unknown	Widespread involvement	Erosions	DIF not performed, diagnosis confirmed with IIF
	56	Female	Unknown	Widespread involvement	Erosions, skin lesions	DIF not performed, diagnosis confirmed with IIF
	38	Female	Unknown	Widespread involvement	Erosions, LP-like white lesions, skin lesions	DIF not performed, diagnosis confirmed with IIF
	51	Female	Unknown	No mucosal lesions	Skin lesions	Speckled pattern of IgG
	22	Female	Unknown	No mucosal lesions	Stomatitis	DIF not performed, diagnosis confirmed with IIF
	67	Male	Unknown	Widespread involvement	Erosions, LP-like lesions	DIF not performed, diagnosis confirmed with IIF
	43	Male	Unknown	No mucosal lesions	None	DIF not performed, diagnosis confirmed with IIF
Lorenzana et al. [21]	54	Female	Caucasian	Buccal mucosa, gingiva, palate	Pain, stomatitis, dry mouth, diffuse erythema, and plaque-like white lesions. Clinical impression: erosive LP	Speckled pattern of IgG (2+)

Table 1 (continued)

Reference	Age	Gender	Race	Location	Clinical presentation	DIF results
Solomon et al. [14]	54	Female	Caucasian	Buccal mucosa	Sore gums, erosive lesions, skin lesions. Clinical impression: erosive LP	Speckled pattern of IgG
	71	Female	Caucasian	Buccal mucosa, gingiva, hard palate	Pain, red gums, xerostomia, desquamation of the oral mucosa, white lichenoid striae. Clinical impression: LP	Speckled pattern of IgG and IgA
	39	Female	Caucasian	Gingiva	Sore gums, erythematous and slightly raised white lesions, white striae, and erosions. Clinical impression: LP	Speckled pattern of IgG
Islam et al. [3]	81	Female	Caucasian	Gingiva, tongue	Pain, erythema, desquamative gingivitis, white striae, erosive lesions. Clinical impression: erosive LP, pemphigoid, pemphigus	Nuclear: Speckled pattern of IgG BMZ: linear band of Fibrinogen
	71	Female	Caucasian	Buccal mucosa, tongue	Painful ulcers, erythema, white striae, erosions. Clinical impression: LM or erosive LP	Speckled pattern of IgG
	75	Female	Caucasian	Tongue, hard palate, gingiva	Pain, ulcers, erythema, white striae	Nuclear: Speckled pattern of IgG BMZ: linear band of Fibrinogen
	40	Female	Caucasian	Buccal mucosa, tongue, buccal vestibule	Pain, erythema, ulcers, white striae	Speckled pattern of IgG
Fourie et al. [15]	42	Female	Unknown	Buccal mucosa	Pain and ulceration, skin lesions. Clinical impression: erosive LP	Nuclear IgG and IgA positivity
Qari et al. [7]	54	Female	Caucasian	Buccal mucosa	Generalized diffuse erythema with white plaque-like lesions	IgG (2+)
	57	Female	Caucasian	Buccal mucosa	Generalized diffuse erythema with white plaque-like lesions	IgG (3+), trace IgM
	73	Female	Caucasian	Labial mucosa	Generalized diffuse erythema with white plaque-like lesions	IgG (2+)
	50	Female	Caucasian	Buccal mucosa	Generalized diffuse erythema with white plaque-like lesions	IgG (2+), trace IgA, IgM (1+), C3 (1+), Fibrinogen (4+)
	49	Female	Caucasian	Gingiva	Generalized diffuse erythema with white plaque-like lesions	IgG (4+)
	60	Female	Caucasian	Gingiva	Generalized diffuse erythema with white plaque-like lesions	IgG (3+), IgA (1+), IgM (1+)
	59	Male	Hispanic	Gingiva	Generalized diffuse erythema with white plaque-like lesions	IgG (3+), trace C3, trace Fibrinogen
	66	Female	Caucasian	Tongue	Generalized diffuse erythema with white plaque-like lesions	IgG (4+), C3 (1+), Fibrinogen (2+)
	28	Female	Unknown	Buccal mucosa	Generalized diffuse erythema with white plaque-like lesions	IgG (2+), trace C3, Fibrinogen (1+)
	66	Female	Caucasian	Buccal mucosa	Generalized diffuse erythema with white plaque-like lesions	IgG (1+), trace C3

Table 1 (continued)

Reference	Age	Gender	Race	Location	Clinical presentation	DIF results
Alshagroud et al. [22]	64	Female	Unknown	Not specified	Clinical impression: LP	Speckled pattern of IgG
	55	Female	Unknown	Not specified	Clinical impression: LP, LM, CUS, VBD	Speckled pattern of IgG
Our series 1	64	Female	Unknown	Gingiva	Burning sensation, positive Nikolsky sign, generalized erythema. Clinical impression: LP, pemphigoid, or pemphigus	Nuclear: Speckled pattern of IgG (3+) BMZ: Fibrinogen (2+)
Our series 2	66	Female	Unknown	Buccal mucosa	White, pain. Clinical impression: LP	Nuclear: Speckled pattern of IgG (2+), trace C3
Our series 3	56	Female	Caucasian	Buccal mucosa	White (cannot be rubbed off), abraded surface, tender to palpation, erythema in biopsy site. Clinical impression: erosive LP or lupus erythematosus	Nuclear: Speckled pattern of IgG (3+) BMZ: Fibrinogen (2+)
Our series 4	57	Female	Caucasian	Gingiva	White, red, purple, ulcerated, erosive, painful, lichenoid lesions. Clinical impression: erosive LP	Nuclear: Speckled pattern of IgG (3+) BMZ: Fibrinogen (3+)
Our series 5	47	Female	Caucasian	Gingiva	Bright red sloughing gingiva and generalized recession. Sensitive on occasion. Clinical impression: LP	Nuclear: Speckled pattern of IgG BMZ: Fibrinogen (2+)
Our series 6	60	Female	Caucasian	Buccal vestibule	Diffuse white striae, erythema. Clinical impression: LP	Nuclear: Speckled pattern of IgG (1+) BMZ: Fibrinogen (3+)
Our series 7	76	Female	Asian	Buccal mucosa	Pain/soreness, red/white. Clinical impression: LP	Nuclear: Speckled pattern of IgG (2+)
Our series 8	76	Female	Caucasian	Buccal mucosa	White and asymptomatic. Clinical impression: LP	Nuclear: Speckled pattern of IgG (2+) BMZ: Fibrinogen (3+)
Our series 9	79	Female	Caucasian	Buccal mucosa	Erythema/localized white; mild, intermittent, discomfort; localized ulceration; prominent positive Nikolsky sign. Clinical impression: LP or pemphigoid	Nuclear: Speckled pattern of IgG (3+) BMZ: C3 (2+)
Our series 10	63	Female	African-American	Gingiva, buccal mucosa	Erythema, pain. Clinical impression: LP	Nuclear: Speckled pattern of IgG BMZ: Fibrinogen (2+)
Our series 11	79	Female	Caucasian	Buccal mucosa	Pain. Clinical impression: erythema multiforme	Nuclear: Speckled pattern of IgG (3+)
Our series 12	54	Female	Caucasian	Buccal mucosa	Red/white erosive lesions, striae present, vesicle formation, pain/burning. Clinical impression: LP or other mucosal pathology	Nuclear: Speckled pattern of IgG (2+) BMZ: Fibrinogen (3+)
Our series 13	59	Female	Caucasian	Gingiva	Sore gums, red/white. Clinical impression: LP	Nuclear: Speckled pattern of IgG BMZ: Fibrinogen (3+)
Our series 14	57	Female	Caucasian	Gingiva	Diffuse, painful ulcers and erythema. Clinical impression: VBD or LP	Nuclear: Speckled pattern of IgG (2+) BMZ: Fibrinogen (1+)

Table 1 (continued)

Reference	Age	Gender	Race	Location	Clinical presentation	DIF results
Our series 15	72	Female	Unknown	Gingiva	Positive Nikolsky sign, red/white, slight sloughing, asymptomatic. Clinical impression: none given	Nuclear: Speckled pattern of IgG (2+) BMZ: Fibrinogen (3+)
Our series 16	83	Female	Caucasian	Gingiva	Red sore gums. Clinical impression: LP	Nuclear: Speckled pattern of IgG (2+)
Our series 17	67	Female	Unknown	Buccal mucosa	White (cannot be rubbed off), eroded surface, blister-like eruptions, no redness. Clinical impression: erosive LP	Nuclear: Speckled pattern of IgG (3+)

BMZ basement membrane zone, *CUS* chronic ulcerative stomatitis, *DEJ* dermoepidermal junction, *DIF* direct immunofluorescence, *IIF* indirect immunofluorescence, *LM* lichenoid mucositis, *LP* lichen planus, *VBD* vesiculobullous disease

Table 2 Ethnic distribution of CUS lesions

Race	Our series (n = 17) (%)	Literature (n = 52) (%)	Our series + literature (n = 69) (%)
Caucasian	65	50	54
Not Specified	24	46	41
African-American	6	2	3
Asian	6	0	1
Hispanic	0	2	1

Table 3 Summary of representative percentages of various locations of the lesion

Location	Our series (n = 17) (%)	Literature (n = 52) (%)	Our series + literature (n = 69) (%)
Buccal mucosa	53	37	41
Gingiva	47	27	32
Tongue	0	31	23
Not specified	0	25	19
Labial mucosa	0	15	12
Hard palate	0	10	7
Buccal vestibule	6	2	3

C3 can also be positive [7], but none of our cases were positive for IgA or IgM. Cases have been reported with IgA and IgM positivity in the literature [1, 7, 8, 14, 15]. It is unclear if there is any clinical significance with complement components or antibodies other than IgG being positive.

Fibrinogen was present 65% in our series, but also 25% in the literature as a whole. Fibrinogen positivity would be an important factor in classifying this disease as a lichenoid mucositis. DIF studies of OLP show deposition of fibrinogen at the basement membrane zone (BMZ) in a shaggy pattern [23]. Unfortunately, in our case series the pattern of fibrinogen deposition at the BMZ was not specified during reporting. It is unclear if the fibrin deposits were shaggy and irregular similar to OLP or a non-specific fibrin exudation secondary to inflammation [13]. Future studies detailing the pattern of fibrin deposition in CUS would be helpful in determining whether the pattern would be a useful diagnostic feature of CUS.

There has been some debate about whether CUS should be considered a distinct entity or a variation of OLP [2, 24, 25]. While the results of our study can neither support nor deny either theory, it raises the question of whether CUS is actually a rare entity or if it is commonly misdiagnosed. As previously mentioned, CUS and erosive OLP have overlapping clinical and histologic features. The best method for distinguishing cases of erosive OLP from CUS is through

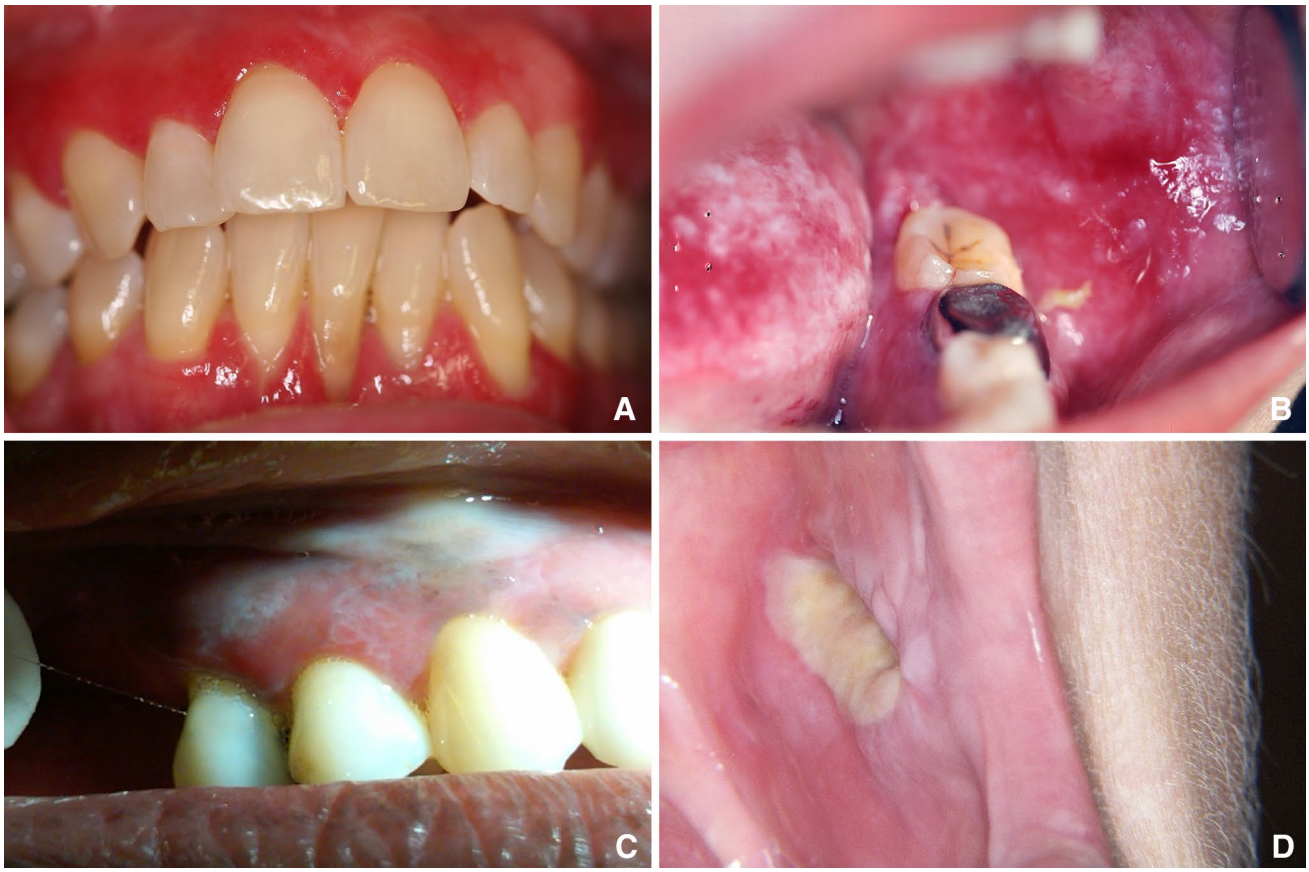

Fig. 1 Clinical examples of CUS **a** Diffuse gingival erythema **b** Zones of erythema and streaky keratosis on the dorsum of the tongue and left buccal mucosa **c** Multiple lesions on the gingiva that have a white border and are well-demarcated **d** Ulcer on the left buccal mucosa

Table 4 Clinical presentation of CUS lesions

Clinical presentation	Our series (n = 17) (%)	Literature (n = 52) (%)	Our series + literature (n = 69) (%)
Ulcerations/erosions	35	65	58
Erythema	76	37	46
Leukoplakia	65	40	46
Pain/burning	76	29	41
Skin lesions	0	25	19
Striae	12	13	13
Blisters/positive Nikolsky sign	29	4	10
Desquamative gingivitis	12	6	7
Stomatitis	0	6	4
Xerostomia	0	4	3
Recession	6	0	1
Ocular involvement	0	2	1

DIF testing, as it remains the gold standard for diagnosing cases of CUS [7].

It is important to distinguish CUS from OLP and vesiculobullous diseases (VBD) because generally CUS is refractory to corticosteroid therapy [2–7, 9, 14]. The recommended treatment is with the antimalarial agent hydroxychloroquine, which is associated with several serious side effects including gastrointestinal symptoms, agranulocytosis,

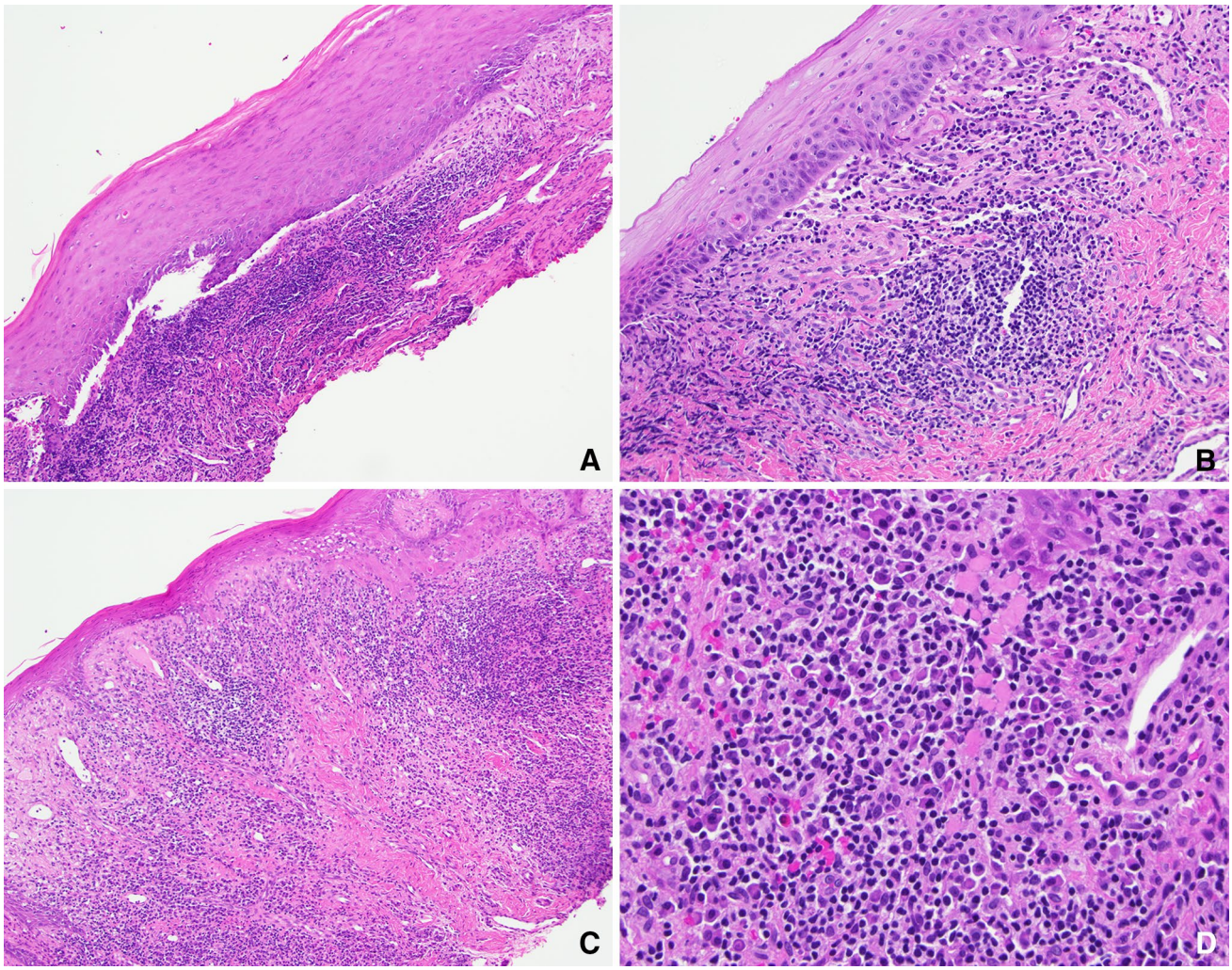

Fig. 2 Histologic features of CUS **a** Epithelial separation from the underlying connective tissue (H&E 10×) **b** Atrophic epithelium (H&E 20×) **c** Low-power view showing chronic inflammatory infiltrate (H&E 10×) **d** High-power view showing inflammatory infiltrate consisting of plasma cells and lymphocytes (H&E 40×)

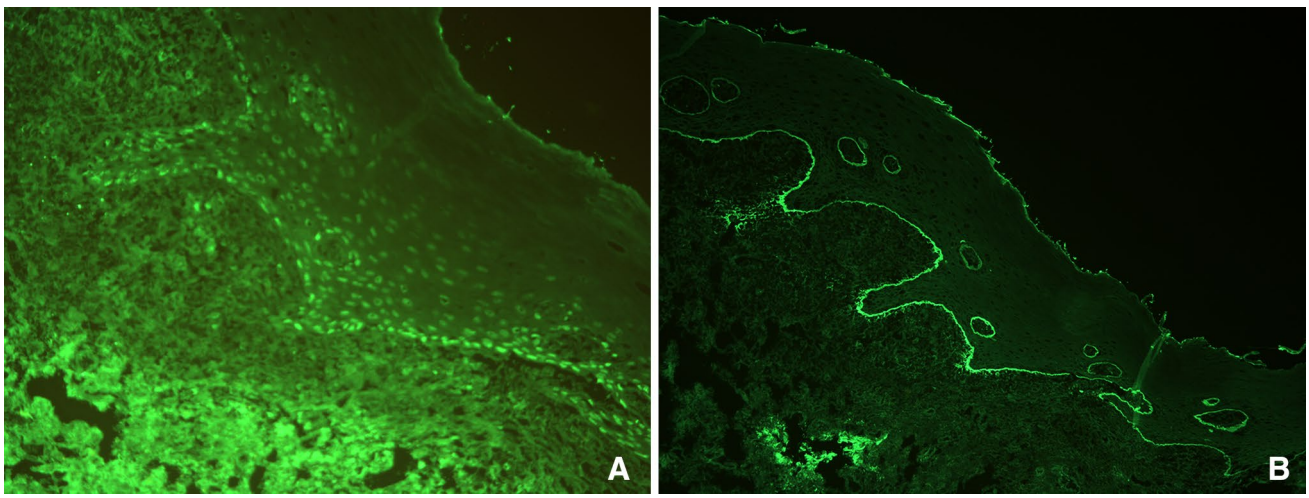

Fig. 3 Direct immunofluorescence from one of our cases exhibiting: **a** Speckled positivity for IgG (20×) **b** Linear basement membrane positivity for fibrinogen (10×)

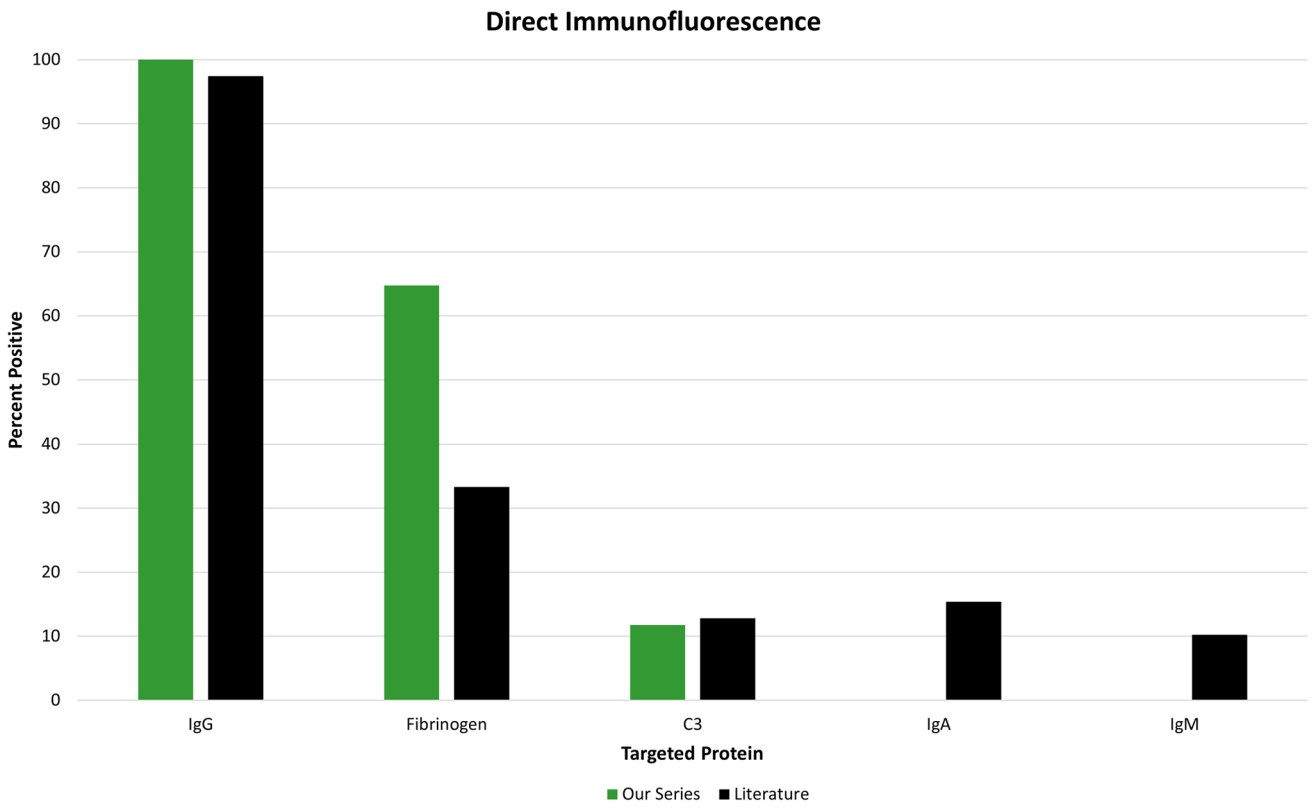

Fig. 4 Distribution of direct immunofluorescence results

aplastic anemia, toxic psychosis, neuromyopathy, and irreversible retinopathy [2, 14].

Conclusion

CUS has an array of clinical presentations that are similar to both OLP and VBD. Although cases are consistently positive on DIF for IgG in a SES-ANA pattern, our series and other cases in the literature show that other antibodies, fibrinogen, and complement components can be present as well. However, it is unclear if any clinical significance can be established with other less frequently positive antibodies, fibrinogen, or complement components.

Since CUS has overlapping clinical, histological, but unique differentiating immunofluorescence features from OLP and VBD, oral healthcare clinicians and pathologists should be sentient of this unusual, but significant, entity when long-standing, recalcitrant, or refractory oral ulcerative diseases with mixed features are encountered. This suspicion should be confirmed by ordering DIF antibody studies. Further studies to define this clinically and immunopathologically diverse entity are highly desirable.

Funding No funding sources were necessary for this project.

Compliance with Ethical Standards

Conflict of interest The authors report no conflicts of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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