Received: 27 March 2018 | Revised: 23 September 2018 | Accepted: 11 October 2018

DOI: 10.1111/odi.13001

REVIEW ARTICLE

WILEY ORAL DISEASES

Chronic ulcerative stomatitis: A comprehensive review and proposal for diagnostic criteria

Lorenzo Azzi[1] | Michele Cerati[2] | Maurizio Lombardo[3] | Maria Pellilli[2] | Fabio Croveri[1] | Vittorio Maurino[1] | Angelo Tagliabue[1] | Lucia Tettamanti[1] | Malgorzata Olszewska[4]

[1]Unit of Oral Pathology, Dental Clinic, ASST Sette Laghi, Ospedale di Circolo, Department of Medicine and Surgery, University of Insubria, Varese, Italy

[2]Unit of Anatomical Pathology, ASST Sette Laghi, Ospedale di Circolo, Varese, Italy

[3]Unit of Dermatological Diseases, ASST Sette Laghi, Ospedale di Circolo, Varese, Italy

[4]Department of Dermatology, Medical University of Warsaw, Warsaw, Poland

Correspondence
Lorenzo Azzi, Unit of Oral Pathology, Dental Clinic, ASST Sette Laghi, Ospedale di Circolo, Department of Medicine and Surgery, University of Insubria, Varese, Italy.
Email: lorenzoazzi86@hotmail.com

Abstract

Chronic ulcerative stomatitis (CUS) is an immune-mediated disorder characterized by oral erosions and ulcers usually refractory to conventional treatments. The disease often involves middle-aged and older women with painful lesions sometimes resembling those of erosive oral lichen planus (OLP). The most affected sites are the buccal mucosa, the gingiva and the tongue, but the skin is involved in 22.5% of cases. Histopathologic features in CUS are non-specific and indistinguishable from those of OLP, with the exception of the presence of a mixed infiltrate composed of lymphocytes and plasma cells. Direct immunofluorescence (DIF) analysis reveals the presence of stratified epithelium-specific antinuclear antibodies (SES-ANA) in the lower third of the epithelium. The IgG antibodies detected on DIF are directed against the ΔNp63α isoform of p63 expressed in the nuclei of the epithelial basal cells. A distinguishing feature of CUS is the low response to conventional corticosteroid therapy and the good outcome with hydroxychloroquine at the dosage of 200 mg/day or higher dosages. This paper presents a comprehensive review of CUS and is accompanied by a new case report (the 73rd case) and a proposal for updated diagnostic criteria.

KEYWORDS

ΔNp63α, chronic ulcerative stomatitis, CUSP antigen, hydroxychloroquine, oral lichen planus, SES-ANA

1 | INTRODUCTION

Chronic ulcerative stomatitis (CUS) is a painful chronic ulcerative process that occurs in the mouth but can occasionally be associated with skin lesions. CUS is defined as an immune-mediated disorder characterized by oral erosions and ulcers that are usually refractory to conventional treatments (Qari, Villasante, Richert, Rees, & Kessler, 2015).

This condition was originally described by Jaremko et al. (1990) and Parodi and Cardo (1990) as being similar to erosive oral lichen planus (OLP) but associated with an antinuclear autoantibody mostly recognized as a specific immunological marker, that is, *stratified epithelium-specific antinuclear antibody* (SES-ANA).

To date, 72 cases have been reported (Alshagroud, Neiders, Kramer, & Suresh, 2017; Beutner et al., 1991; Chorzelski, Olszewska, Jarząbek-Chorzelska, & Jablońska, 1998; Church & Schosser, 1992; Fourie, van Heerden, McEachen, & van Zyl, 2011; Islam et al., 2007; Jaremko et al., 1990; Kapińska-Mrowiecka, Czubak-Macugowska, Michcik, Chomik, & Wlodarkiewicz, 2010; Ko, Danciu, Fullen, & Chan, 2018; Lewis, Beutner, Rostami, &

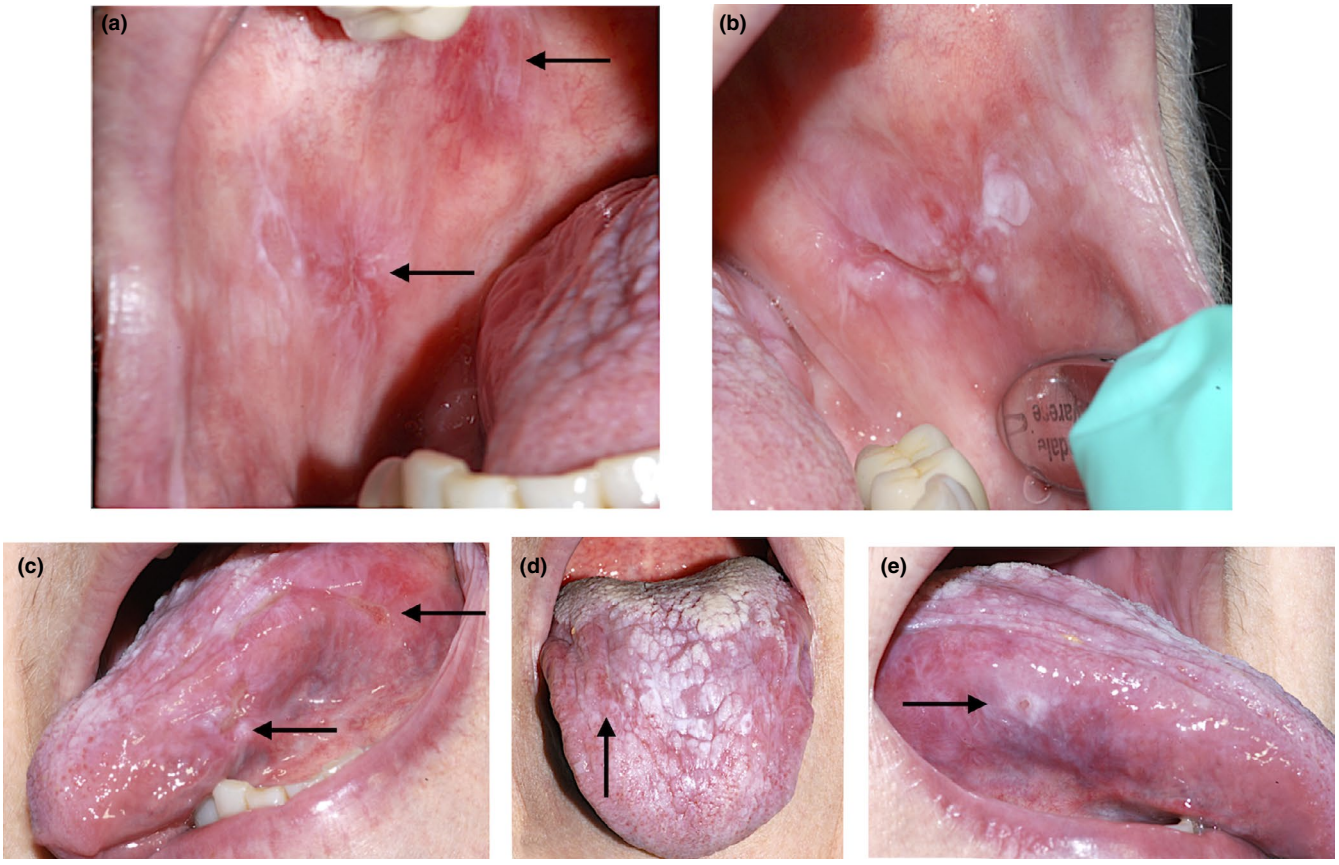

FIGURE 1 The 73rd *case report*. A 54-year-old Caucasian woman with diffuse oral ulcerations with white striae resembling erosive OLP. (a) Right side of the buccal mucosa: two ulcerations with lichenoid appearance (arrows); (b) left side of the buccal mucosa: linear ulceration with white striae departing from the border; (c) left lateral border of the tongue: two painful linear ulcerations (arrows); (d): dorsum of the tongue: small ulcer surrounded by a wide plaque-like white lesion resembling that of hyperplastic OLP (arrow); (e): right lateral border of the tongue: an ulcerative lesion surrounded by white striae (arrow)

Chorzelski, 1996; Lorenzana, Rees, Glass, & Detweiler, 2000; Molenda & Kozlowski, 2014; Parodi & Cardo, 1990; Qari et al., 2015; Reddy, Fitzpatrick, Bhattacharyya, Cohen, & Islam, 2018; Solomon et al., 2003; Wörle et al., 1997). However, a literature review has indicated that its prevalence in the general population could be underestimated (Solomon, 2008).

The distinguishing features of the disease are a low response to corticosteroid therapy and good outcomes with antimalarials,

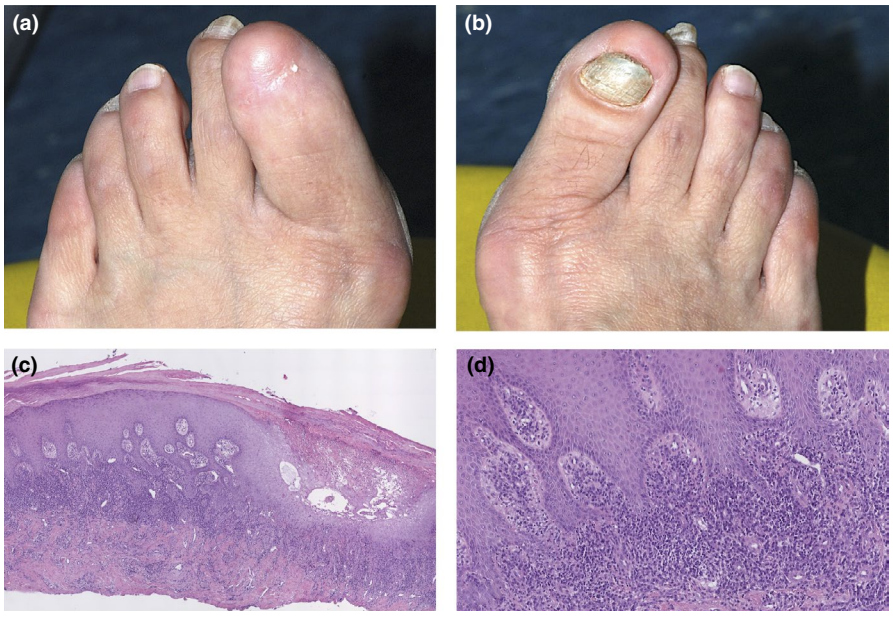

FIGURE 2 Cutaneous lesions involving the left foot hallux. (a) A LP lesion on the left foot was diagnosed histopathologically 13 years prior to the visit; the surgical treatment of this lesion resulted in loss of the nail of the hallux; (b) onychodystrophy is observed on the other fingernails; (c) cutaneous biopsy of a foot lesion conducted 13 years before oral involvement. H&E 40X showed psoriatic orthokeratosis with preservation of the stratum granulosum, ulceration on the right side of the picture with zonal exocytosis and a band-like lichenoid infiltrate at the dermo-epidermal junction; (d) increased magnification; H&E 130X shows a mixed infiltrate composed of lymphocytes and plasma cells

especially hydroxychloroquine, either alone or in combination with corticosteroids.

This paper presents a comprehensive review of CUS along with a new case report (the 73rd case) and a proposal for updated diagnostic criteria.

2 | CASE REPORT

A 54-year-old Caucasian woman visited our hospital complaining of a chronic painful sensation in her mouth, which she described as burning and stinging.

She also reported a several-month history of difficulty eating.

Oral examination revealed the presence of multiple erosive and ulcerative lesions surrounded by white hyperkeratotic striae resembling those of erosive OLP (Figure 1).

These ulcers were detected on the buccal mucosa, the floor of the mouth, and the lateral borders and ventral aspect of the tongue.

Ulcerative lesions were also observed on the dorsum of the tongue, and the surrounding mucosa exhibited a plaque-like lichenoid appearance. While the gingiva was not involved, a red erosive lesion was detected on the keratinized mucosa of the hard palate where a removable partial prosthesis was resting, thus mimicking denture stomatitis.

Several teeth had been covered with fixed prostheses placed several years prior to this visit.

The patient's medical history revealed a stroke 2 years prior, and the patient was taking clopidogrel, gabapentin and bromazepam.

Moreover, an LP lesion on her left foot was diagnosed histopathologically 13 years earlier; the surgical treatment of this lesion resulted in loss of the nail on her hallux (Figure 2). No other cutaneous lesions were discovered at the time of her visit for oral symptoms.

The haematochemical results were negative, with the exception of mild lymphocytosis and the presence of low-titre ANAs (i.e., 1:80) detected on a HEp-2 cell substrate.

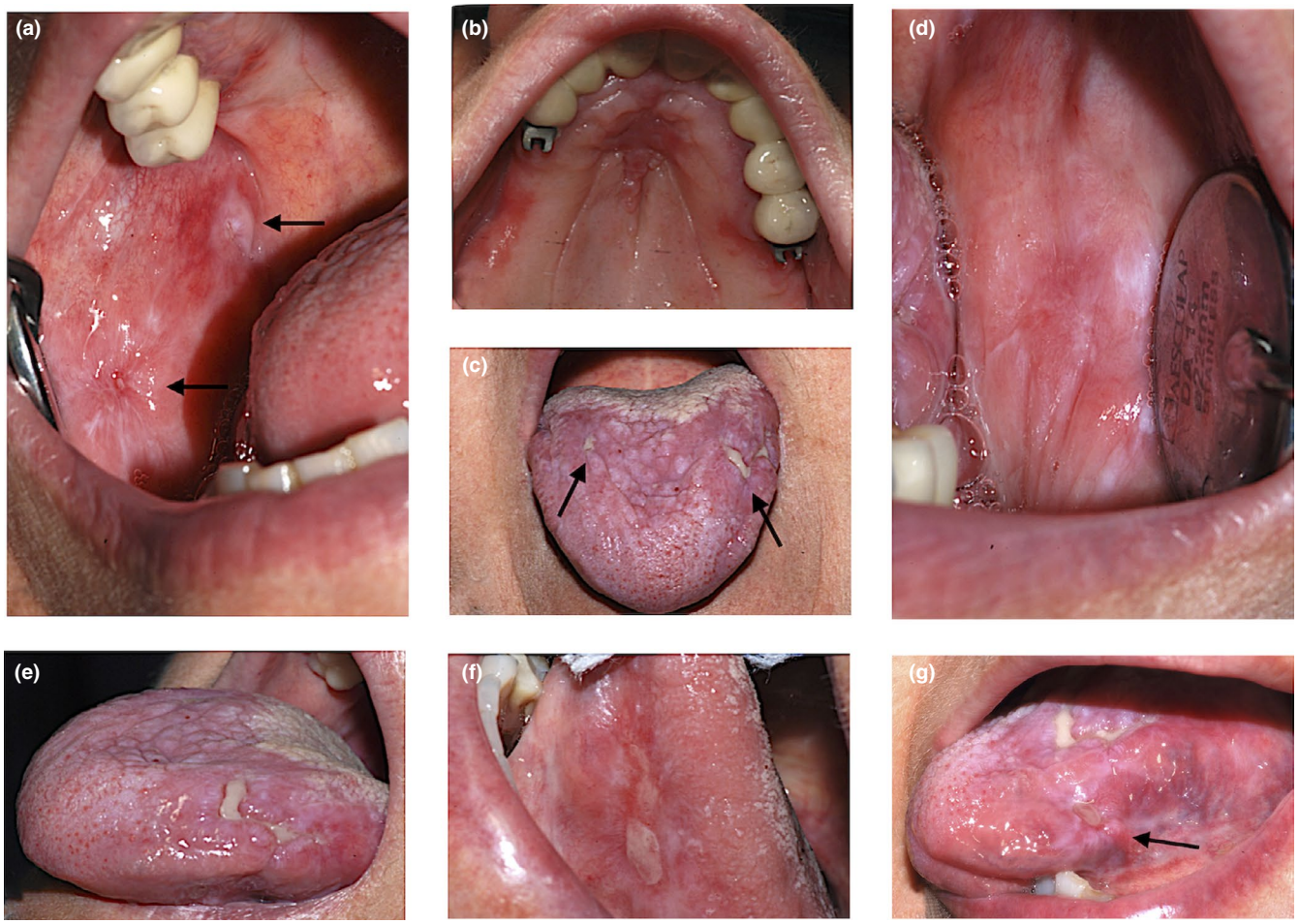

FIGURE 3 Clinical appearance of the lesions after corticosteroid therapy. Lesions did not recover, in fact they worsened. (a) Right side of the buccal mucosa: two ulcerations with white striae departing from their border (arrows); (b) erosive and erythematous lesions of the hard palate and edentulous ridges; (c) ulcerations surrounded by a plaque-like infiltrating lichenoid lesion on the dorsum of the tongue (arrows); (d) left side of the buccal mucosa: lichenoid erosions with a small ulceration; (e–g) lichenoid ulcerations on left lateral border and ventral aspect of the tongue

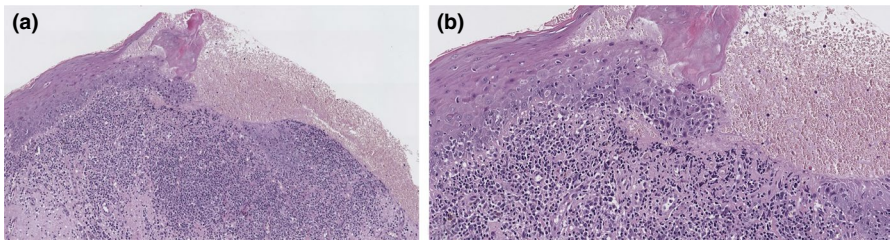

FIGURE 4 Histopathological features of the oral lesions. (a) Oral biopsy, conducted when oral involvement started (H&E 40X), revealed the presence of lichenoid stomatitis with mild epithelial atrophy, partial darkening of the chorion–epithelial junction and ulceration on the right side of the picture with underlying granulation tissue; (b) increased magnification (H&E 200X) revealed a recognizable mixed infiltrate composed of lymphocytes and plasma cells, scattered Civatte bodies and exocytosis near the ulcer

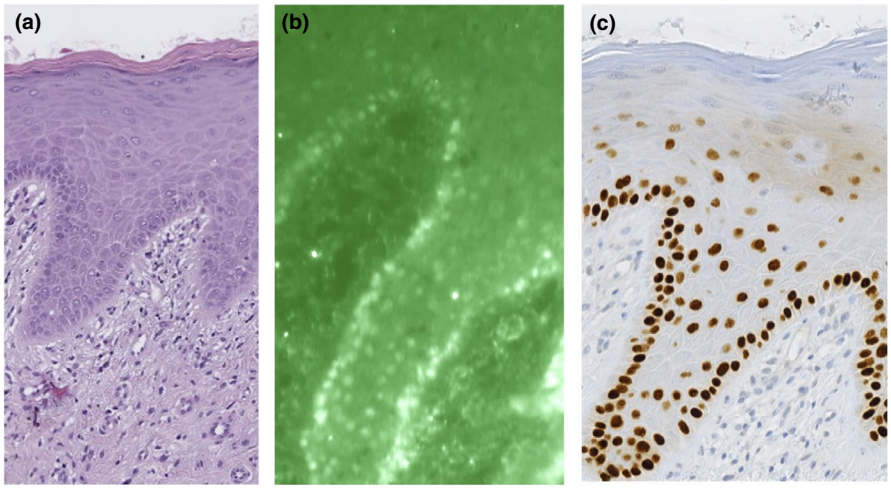

FIGURE 5 DIF analysis. (a) H&E, 200X. The zone where DIF was performed. (b) DIF, 200X. Deposition of IgG antibodies in the lower third of the epithelium with a speckled pattern (IgA, IgM and C3 findings were negative). (c) IHC, 200X. Immunohistochemical analysis with anti-p63 antibody showed results very similar to those of DIF, underlying that the ΔNp63α isoform of p63 is the typical antigen in CUS

An incisional biopsy was performed on the left buccal mucosa, and histopathological analysis revealed the presence of lichenoid stomatitis. A skin patch test was prescribed to exclude allergies to dental materials due to the presence of many restorations and of the removable prosthesis, but these test results were negative.

The patient was initially administered salivary substitutes and 2% miconazole oral gel to treat an eventual Candida superinfection. However, this approach was not effective, even on the hard palate. A 0.05% topical clobetasol ointment was prescribed for 1 month, but the lesions did not show any clinical signs of improvement.

Due to the failure of topical corticosteroid therapy, the patient underwent a dermatological consultation, and the clinician prescribed systemic betamethasone followed by systemic prednisone in association with topical triamcinolone. The patient experienced a frustrating therapeutic failure.

Subsequent efforts to control the disease and improve the oral lesions with systemic azathioprine and methotrexate were not successful (Figure 3).

At this point, the incisional biopsy was repeated, and multiple bioptical specimens were collected from the left lateral border of the tongue and the right buccal mucosa. This time, fresh samples were also analysed by direct immunofluorescence (DIF).

Haematoxylin and eosin (H&E) staining confirmed the presence of lichenoid stomatitis, with an admixed subepithelial inflammatory infiltrate composed of lymphocytes and plasma cells, as well as epithelial atrophy, scattered Civatte bodies and occasional exocytosis near the ulceration (Figure 4).

The skin biopsy of the foot performed several years earlier was reviewed and showed lichenoid band-like inflammation with lymphocytes and plasma cells, closely resembling the inflammatory infiltrate detected in the oral cavity (Figure 2).

Interestingly, DIF of the oral lesions revealed the presence of IgG antibodies against the nuclei of epithelial cells in the lower third of the epithelium, while the results for IgA and IgM antibodies and C3 were negative (Figure 5).

Together, the clinical appearance of the disease, the low response to corticosteroid and immunosuppressive therapy, and the finding of stratified epithelium-specific antinuclear antibody (SESANA) by DIF analysis led to the final diagnosis of CUS.

Systemic corticosteroid treatment was interrupted, and hydroxychloroquine was prescribed at a dosage of 400 mg/day. After one month, the ulcers were completely cleared from the oral mucosa and only thin, asymptomatic hyperkeratotic striae remained (Figure 6).

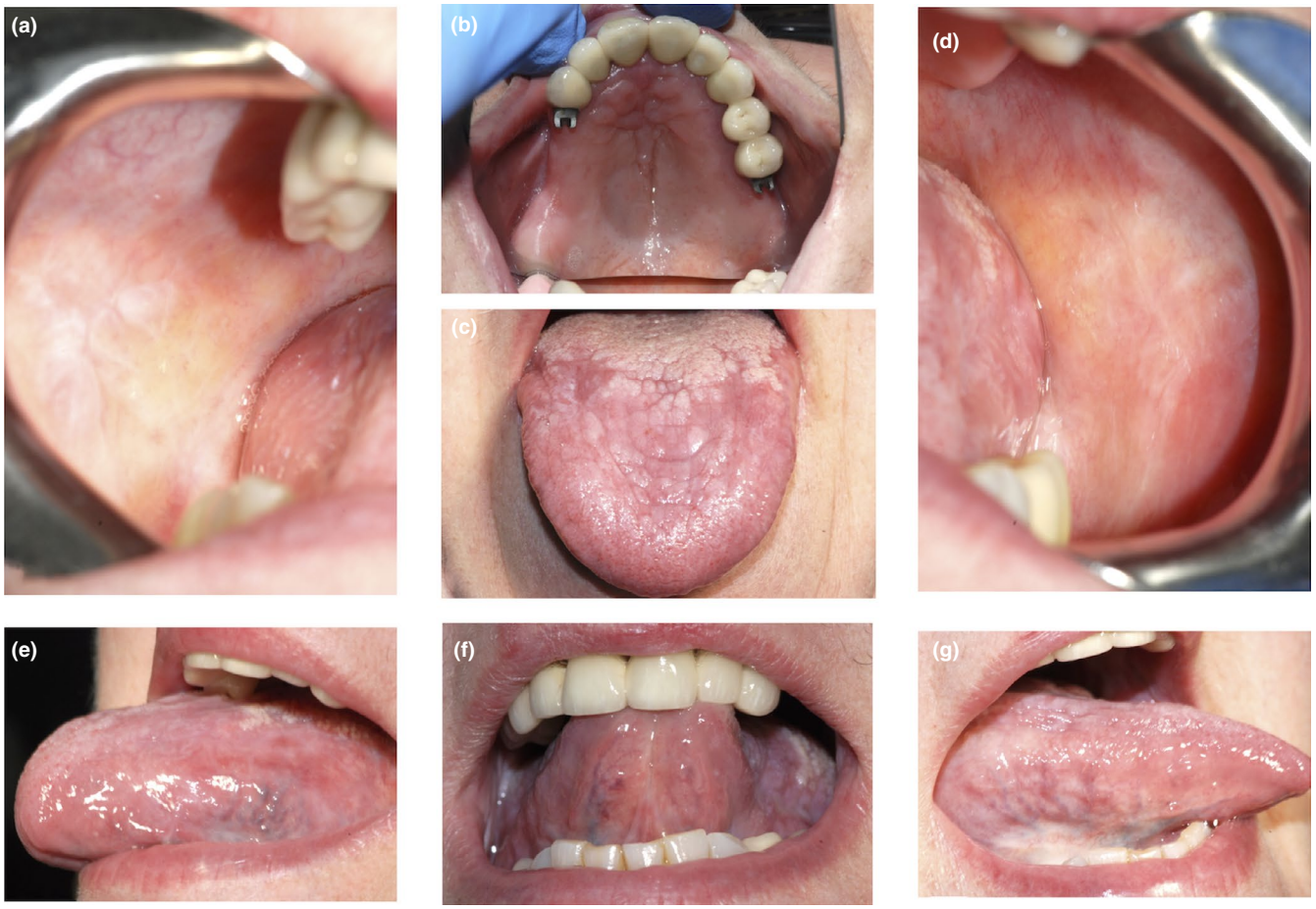

FIGURE 6 Lesional healing after 1 month of treatment with hydroxychloroquine (Plaquenil) at 400 mg/day. (a) Right side of the buccal mucosa; (b) hard palate and edentulous ridges; (c) dorsum of the tongue; (d) left side of the buccal mucosa; (e–g) lateral borders and ventral aspect of the tongue. The patient did not experience important relapses after a follow-up period of 1 year

After 1 year of treatment with hydroxychloroquine, the patient experienced only scattered, mild relapses during seasonal changes, but these relapses quickly resolved after the topical application of 0.05% clobetasol ointment.

This is the 73rd clinical case of CUS reported in the literature and provides images of the lesions after each therapeutic step, highlighting the low response to corticosteroid therapy and the dramatic positive effect of the antimalarial treatment. This positive effect is a distinguishing feature of the disease that can facilitate its differentiation from classic erosive OLP.

The diagnosis required 2 years from the initial oral presentation to the clinical suspicion of CUS, and this process was frustrating for both the clinicians and the patient.

In hindsight, the cutaneous lesion that preceded the oral manifestation could be considered the first manifestation of this disease or a related lesion. Several studies in the literature have reported cutaneous manifestations that could be associated or might even precede the oral manifestation of this disease.

Consequently, the term CUS may be inappropriate for describing a mucocutaneous disorder in which the cutaneous district is often an important component of the clinical manifestation.

3 | REVIEW

3.1 | Epidemiology

Due to the low number of reported cases and the clinical overlap with erosive OLP, data regarding the prevalence of CUS in the general population are lacking.

However, some useful information may be recovered from the literature (Table 1).

Chronic ulcerative stomatitis mainly affects women (68/73 cases, i.e., 93.15%), especially Caucasian women (55/58, i.e., 94.83%). However, CUS in 2 Black women and 1 Asian woman has been reported (Jaremko et al., 1990; Reddy et al., 2018).

In contrast, only five males with CUS have been described (5/73, i.e., 6.85%), mostly Caucasian males.

The age of CUS patients ranged from 28 to 86, but most of them were middle-aged or older women, with a mean age at diagnosis of 62.15 ± 12.3 years.

It should be highlighted that the mean age at disease onset (56.83 ± 14.2 years) was usually different from the age at diagnosis, underlying a very common diagnostic delay in this disease. In fact, focusing on the 26 patients for whom the age at both onset and diagnosis is available, the mean diagnostic delay was 6.31 years, with a range

TABLE 1 Demographic and epidemiological data on the 73 cases of CUS described in the literature

Authors	Year	Patients	Sex	Ethnic group	Age at diagnosis	Age at oral onset	Age at extraoral onset
Jaremko WM *et al*	1990	1	F	B	59	58	years before (nos)
		2	F	C	77	77	77
		3	F	C	81	71	n/a
		4	F	C	77	57	
Parodi AP *and* Cardo PP	1990	5	F	C	64	52	63
		6	F	C	53	51	
Beutner EH *et al*	1991	7	F	C	59	35	
		8	F	C	64	44	
(Chorzelski *et al*; Bańka-Wrona A *et al*)	(1998; 2009)	9	F	C	45	43	62
		10	M	C	48	47	
Church LF *and* Schosser RH	1992	11	F	C	71	63	n/a
Lewis JE *et al*	1996	12	F	C	73	42	73
Wörle *et al*	1997	13	F	C	40	29	
Chorzelski TP *et al*	1998	14	F	C	n/a	63	
		15	F	C	n/a	68	
		16	F	C	n/a	56	
		17	F	C	n/a	66	
		18	F	C	n/a	46	50
		19	F	C	n/a	84	80
		20	F	C	n/a	35	n/a
		21	F	C	n/a	75	
		22	F	C	n/a	86	n/a
		23	F	C	n/a	66	
		24	M	C	n/a	48	
		25	F	C	n/a	56	n/a
		26	F	C	n/a	38	n/a
		27	M	C	n/a	67	
Lorenzana ER *et al*	2000	28	F	C	54	51	
Solomon LW *et al*	2003	29	F	C	54	54	38
		30	F	C	71	years before	
Islam MN *et al*	2007	32	F	C	81	n/a	
		33	F	C	71	70	
		34	F	C	75	n/a	
		35	F	C	40	38	
Kapińska-Mrowiecka M *et al*	2010	36	F	C	69	68	68
Fourie J *et al*; Jacyk WK *et al*	2011	37	F	C	42	42	29
Molenda I *and* Kozlowski Z	2014	38	F	C	63	63	
Qari H *et al*	2015	39	F	C	54	n/a	
		40	F	C	57	n/a	
		41	F	C	73	n/a	
		42	F	C	50	n/a	

(Continues)

TABLE 1 (Continued)

Authors	Year	Patients	Sex	Ethnic group	Age at diagnosis	Age at oral onset	Age at extraoral onset
		43	F	C	49	n/a	
		44	F	C	60	n/a	
		45	M	H	59	n/a	
		46	F	C	66	n/a	
		47	F	n/a	28	n/a	
		48	F	C	66	n/a	
Alshagroud R *et al*	2017	49	F	n/a	64	n/a	
		50	F	n/a	55	n/a	
Ko EM *et al*	2018	51	F	C	63	63	
		52	F	n/a	65	65	
		53	M	n/a	61	n/a	
		54	F	n/a	70	67	
		55	F	n/a	86	76	
Reddy R *et al*	2018	56	F	n/a	64	n/a	
		57	F	n/a	66	n/a	
		58	F	C	56	n/a	
		59	F	C	57	n/a	
		60	F	C	47	n/a	
		61	F	C	60	n/a	
		62	F	A	76	n/a	
		63	F	C	76	n/a	
		64	F	C	79	n/a	
		65	F	B	63	n/a	
		66	F	C	79	n/a	
		67	F	C	54	n/a	
		68	F	C	59	n/a	
		69	F	C	57	n/a	
		70	F	n/a	72	n/a	
		71	F	C	83	n/a	
		72	F	n/a	67	n/a	
Azzi *et al* (current paper)	2018	73	F	C	56	54	41

C = Caucasian; B = Black; H = Hispanic; n/a = not available.

of 0–31 years. The final diagnosis was suggested by the low response to corticosteroid therapy, resulting in clinical suspicion of CUS.

Moreover, three patients, including the patient described here, reported cutaneous lesions 16, 13 and 13 years before mucosal involvement, respectively (Fourie et al., 2011; Solomon et al., 2003). Other cases, in contrast, showed cutaneous lesions 4, 11, 18 and even 31 years after the oral involvement (Bańka-Wrona, Kolacińska-Strasz, Labęcka, Kraińska, & Olszewska, 2009; Chorzelski et al., 1998; Lewis et al., 1996; Parodi & Cardo, 1990).

3.2 | Clinical presentation

Patients affected by CUS often complain of oral mucosal pain and discomfort, difficulty eating and unintentional weight loss, with periodic symptom exacerbation and remission (Islam et al., 2007).

In addition, many patients have a long history of suffering from oral pain without diagnosis or effective treatment, with even topical and systemic corticosteroid therapy being ineffective.

On local examination, such patients exhibit painful oral erosions and/or ulcers, which may sometimes appear non-specific. Other times, these ulcers may be indistinguishable from the typical lesions of erosive OLP and be surrounded by white striae (Chorzelski et al., 1998).

Regarding the *topographical distribution*, the most common intraoral sites are the buccal mucosa, the gingiva and the tongue, even though the labial mucosa and hard palate may also be involved (Solomon et al., 2003). In fact, clinical data are available from 63 patients described in the literature, including our patient (Table 2).

Twelve patients (19.05%) exhibited a diffuse distribution of ulcers within the oral cavity, while the remaining 51 patients exhibited lesions confined to specific sites.

TABLE 2 Clinical features of CUS described in the literature

Authors	Patients	Topographic distribution								Extra-oral involvement		
		BM	T	G	LM	HP	Diffuse	Lichen-like	Nikolsky	Skin	Lichen-like	Mucosal involvement
Jaremko WM *et al*	1	x		x				x		scalp scarring alopecia		
	2	x	x	x						toenails shedding		
	3	x	x	x		x				yes (nos)		
	4			x	x					no		
Parodi AP *and* Cardo PP	5	x			x			x		LP arms and legs	x	
	6	x			x			x		no		
Beutner EH *et al*	7			x				x		no		
	8	x	x					x		no		
(Chorzelski *et al*; Bańka-Wrona A *et al*)	9	x	x		x					LP (after 18 years)	x	
	10		x	x					x	no		
Church LF *and* Schosser RH	11			x				x		nail dystrophy		
Lewis JE *et al*	12	x	x					x		axillary and mammarian fold	x	
Wörle *et al*	13		x	x		x			x	no		
Chorzelski TP *et al*	14						x	x		no		
	15						x			no		
	16		x		x					no		
	17		x		x					no		
	18						x		x	Erythema necrolyticum migrans-like		
	19						x			no		conjunctivitis and ectropion
	20						x	x		LP	x	
	21		x		x					no		
	22						x	x		atypical thighs lesions	x	
	23						x			no		
	24						x			no		
	25						x			LP-like	x	
	26						x	x		LP	x	
	27						x	x		no		
Lorenzana ER *et al*	28	x		x		x		x		no		
Solomon LW *et al*	29	x						x		no (but positive in the past)	x	
	30	x		x		x		x		no		

(Continues)

TABLE 2 (Continued)

Authors	Patients	Topographic distribution								Extra-oral involvement		
		BM	T	G	LM	HP	Diffuse	Lichen-like	Nikolsky	Skin	Lichen-like	Mucosal involvement
	31	x		x				x		no		
Islam MN *et al*	32	x	x	x				x		no		
	33	x	x					x		no		
	34	x	x	x				x		no		
	35	x	x	x				x		no		
Kapińska-Mrowiecka M *et al*	36	x			x					violet-coloured papules; alopecia		conjunctivitis
Fourie J *et al*; Jacyk WK *et al*	37	x	x					x		Several ulcers and crusting		
Molenda I *and* Kozlowski Z	38	x	x		x					no		
Qari H *et al*	39	n/a	n/a	n/a	n/a	n/a	n/a	n/a		no		
	40	n/a	n/a	n/a	n/a	n/a	n/a	n/a		no		
	41	n/a	n/a	n/a	n/a	n/a	n/a	n/a		no		
	42	n/a	n/a	n/a	n/a	n/a	n/a	n/a		no		
	43	n/a	n/a	n/a	n/a	n/a	n/a	n/a		no		
	44	n/a	n/a	n/a	n/a	n/a	n/a	n/a		no		
	45	n/a	n/a	n/a	n/a	n/a	n/a	n/a		no		
	46	x	x					x		no		
	47	x		x				x		no		
	48	n/a	n/a	n/a	n/a	n/a	n/a	n/a		no		
Alshagroud R *et al*	49	n/a	n/a	n/a	n/a	n/a	n/a	x		n/a		
	50	n/a	n/a	n/a	n/a	n/a	n/a	x		n/a		
Ko EM *et al*	51			x					x	no		
	52	x		x[a]				x		no		
	53			x						no		
	54			x				x		no		
	55	x		x				x		no		
Reddy R *et al*	56			x					x	no		
	57	x						x		no		
	58	x						x		no		
	59			x				x		no		
	60			x				x		no		
	61	x						x		no		

(Continues)

TABLE 2 (Continued)

Authors	Patients	Topographic distribution							Extra-oral involvement		
		BM	T	G	LM	HP	Diffuse	Lichen-like	Nikolsky	Skin	Lichen-like	Mucosal involvement
	62	x						x		no		
	63	x						x[b]		no		
	64	x							x	no		
	65	x		x				x		no		
	66	x								no		
	67	x							x	no		
	68			x				x		no		
	69			x						no		
	70			x					x	no		
	71			x				x		no		
	72	x							x	no		
Azzi L *et al* (current paper)	73						x	x		foot lesions	x	

BM = buccal mucosa; T = tongue; G = gingiva; LM = labial mucosa; HP = hard palate; n/a = data not available.
[a]Edentulous alveolar ridges. [b]White and asymptomatic lesions.

The buccal mucosa was the most common site and was involved in 64.71% of these cases, followed by the gingiva (54.9%), especially on the maxillary aspect, and by the tongue (33.33%), which showed involvement of the ventral aspect and lateral borders. In some cases, including our patient, lesions were also observed on the dorsum of the tongue.

Gingival lesions appeared clinically in the form of desquamative gingivitis, thus mimicking erosive OLP or mucous membrane pemphigoid (MMP), with non-specific lesions or the presence of lichenoid white plaques or striae.

Buccal, gingival and lingual lesions are often associated, but gingival lesions can also occur alone, presenting a diagnostic challenge in differentiating CUS from other gingival immunological pathoses (Glickman & Smulow, 1964).

Less frequently involved sites were the labial mucosa (17.65% of cases) and the hard palate (7.84%): these sites were usually associated with the more common ones.

Interestingly, no lesions have been reported to occur in the soft palate or oropharynx.

Regarding the *clinical appearance* of CUS lesions, they are mostly symmetrical and sometimes present a lichenoid appearance, for example, white striae departing from the borders of the ulcers (60% of cases). Other lesions may appear non-specific: a few patients have shown an asymmetrical distribution and single-site involvement. In nine cases, vesicles and Nikolsky's sign were observed (Beutner et al., 1991; Chorzelski et al., 1998; Ko et al., 2018; Reddy et al., 2018; Wörle et al., 1997).

Despite the term CUS, extra-oral involvement was not uncommon (23.94% of cases). The skin was involved in almost all cases (22.54%), while two case reports described ocular manifestations, such as conjunctivitis and ectropion (Chorzelski et al., 1998; Kapińska-Mrowiecka et al., 2010), and one case reported genital lesions (Chorzelski et al., 1998).

In the 16 cases with cutaneous involvement, skin lesions resembling LP or presenting a lichenoid appearance were observed in nine cases (i.e., 56.25%), while other lesions appeared to be non-specific, such as scalp scarring alopecia or ungueal dystrophy. The association was less evident for these lesions than for those with a lichenoid appearance, and the relation was probably accidental for some (Chorzelski, 1990).

Interestingly, all extraoral manifestations of the disease occurred in women, and cutaneous manifestations with lichenoid features were associated with a more diffuse distribution of the oral lesions, which highlights the more severe clinical behaviour of apparent lichenoid cases.

Overall, it should be noted that in several cases, cutaneous lesions preceded or followed mucosal involvement by many years, which again demonstrates how the term CUS is inadequate for this condition.

3.3 | Histopathology

The histopathological (H&E) findings of CUS are non-specific and could very often be misinterpreted as OLP by pathologists.

TABLE 3 Histopathological findings and DIF analysis results of CUS patients

			Histopathological features		DIF analysis						
Authors	Patients	Specimen	H&E	Inflammatory components	IgG	IgA	IgM	C3	Pattern	Extension	Fibrinogen BMZ
Jaremko WM et al.	1	MC	Lichenoid [M]; non-specific [C]; hd	Lymphocytes, histiocytes	pos (++)	pos (+)	neg	neg	Speckled	Lower third	pos (++)
	2	M	Lichenoid; hd	Lymphocytes, neutrophils	pos (++)	pos (+)	neg	neg	Speckled	Lower third	pos (++)
	3	MC	Lichenoid; hd	Lymphocytes, plasma cells	pos (++)	neg	neg	neg	Speckled	Lower third	pos (+)
	4	M	Lichenoid; hd	Lymphocytes, plasma cells	pos (++)	neg	neg	neg	Speckled	Lower third	pos (++)
Parodi AP and Cardo PP	5	C	Lichenoid	Lymphocytes	pos	n/a	pos (BMZ)	pos[a]	Speckled	Lower third	n/a
	6	M	Lichenoid [M]	Lymphocytes	pos	n/a	n/a	n/a	Speckled	Lower third	pos
Beutner EH et al.	7	M	Lichenoid	Lymphocytes, plasma cells[a]	pos	n/a	n/a	n/a	Speckled	Lower third	n/a
	8	M	n/a	n/a	pos	n/a	n/a	n/a	Speckled	Lower third	n/a
(Chorzelski et al., Bańka-Wrona A et al.)	9	M (and C[b])	Non-specific (lichenoid LP)	(Lymphocytes)	pos	n/a	n/a	n/a	Speckled	Lower third	n/a
	10	M	n/a	n/a	pos	n/a	n/a	n/a	Speckled	Lower third	n/a
Church LF and Schosser RH	11	M	Lichenoid; hd	Lymphocytes	pos	n/a	n/a	n/a	Speckled	Lower third	pos
Lewis JE et al.	12	MC	Lichenoid; hd	Lymphocytes, plasma cells, histiocytes	pos	n/a	n/a	n/a	Speckled	Lower third	pos
Wörle et al.	13	MC	Non-specific; hd	Lymphocytes, histiocytes	neg	neg	neg	neg	neg	neg	neg
Chorzelski TP et al.	14	n/a	n/a	n/a	np	np	np	np	np	np	np
	15	n/a	n/a	n/a	np	np	np	np	np	np	np
	16	n/a	n/a	n/a	pos	n/a	n/a	n/a	Speckled	Lower third	n/a
	17	n/a	n/a	n/a	np	np	np	np	np	np	np
	18	n/a	n/a	n/a	np	np	np	np	np	np	np
	19	MM	n/a	n/a	pos	n/a	n/a	n/a	Speckled	Lower third	n/a
	20	C	Lichenoid (LP) [C]	n/a	np	np	np	np	np	np	np
	21	n/a	n/a	n/a	pos	n/a	n/a	n/a	Speckled	Lower third	n/a
	22	C	Non-specific	n/a	np	np	np	np	np	np	np
	23	n/a	n/a	n/a	np	np	np	np	np	np	np
	24	n/a	n/a	n/a	np	np	np	np	np	np	np
	25	C	Lichenoid (LP) [C]	n/a	np	np	np	np	np	np	np
	26	C	Lichenoid (LP) [C]	n/a	np	np	np	np	np	np	np
	27	n/a	n/a	n/a	np	np	np	np	np	np	np

(Continues)

TABLE 3 (Continued)

			Histopathological features		DIF analysis						
Authors	Patients	Specimen	H&E	Inflammatory components	IgG	IgA	IgM	C3	Pattern	Extension	Fibrinogen BMZ
Lorenzana ER et al.	28	M	Lichenoid; hd	Lymphocytes, plasma cells	pos (++)	n/a	n/a	n/a	Speckled	Lower third	n/a
Solomon LW et al.	29	M	Non-specific	n/a	pos	n/a	n/a	n/a	Speckled	Lower third	n/a
	30	M	Lichenoid; hd	Lymphocytes, plasma cells	pos	pos	n/a	n/a	Speckled	Lower third	n/a
	31	M	Non-specific	Lymphocytes, plasma cells (deep)	pos	n/a	n/a	n/a	Speckled	Lower third	n/a
Islam MN et al.	32	M	Lichenoid	Lymphocytes, plasma cells	pos	neg	neg	neg	Speckled	Lower third	pos
	33	M	Lichenoid	Lymphocytes, plasma cells, neutrophils (ulcer)	pos	neg	neg	neg	Speckled	Lower third	neg
	34	M	Lichenoid	Lymphocytes, plasma cells	pos	neg	neg	neg	Speckled	Lower third	pos
	35	M	Lichenoid	Lymphocytes, plasma cells, neutrophils (ulcer)	pos	neg	neg	neg	Speckled	Lower third	neg
Kapińska-Mrowiecka M et al.	36	MC	Non-specific [M]; lichenoid LP [C]	Lymphocytes	neg	n/a	n/a	n/a	neg	neg	n/a
Fourie J et al., Jacyk WK et al.	37	MC	Non-specific [M]; lichenoid [C]	Lymphocytes, plasma cells [M], mast cells [M], histiocytes	pos	pos	n/a	n/a	Speckled	Lower third	n/a
Molenda I and Kozlowski Z	38	M	Non-specific	Lymphocytes, plasma cells, neutrophils	pos	neg	n/a	neg	Speckled	Lower third	n/a
Qari H et al.	39	M	Lichenoid; hd	Lymphocytes, plasma cells	pos (++)	neg	neg	neg	Speckled	Lower third	neg
	40	M	Non-specific; hd	Lymphocytes, plasma cells	pos (+++)	neg	Trace	neg	Speckled	Lower third	neg
	41	M	Lichenoid (OLP); hd	Lymphocytes	pos (++)	neg	neg	neg	Speckled	Lower third	neg
	42	M	Lichenoid (OLP); hd	Lymphocytes	pos (++)	trace	pos (+)	pos (+)	Speckled	Lower third	pos (++++)
	43	M	Lichenoid (OLP); hd	Lymphocytes, plasma cells	pos (++++)	neg	neg	neg	Speckled	Lower third	neg
	44	M	Non-specific; hd	Lymphocytes, plasma cells	pos (+++)	pos (+)	pos (+)	neg	Speckled	Lower third	neg
	45	M	Lichenoid (OLP); hd	Lymphocytes, plasma cells	pos (+++)	neg	neg	Trace	Speckled	Lower third	Trace
	46	M	Lichenoid (OLP); hd	Lymphocytes, plasma cells	pos (++++)	neg	neg	pos (+)	Speckled	Lower third	pos (++)
	47	M	Lichenoid; hd	Lymphocytes, plasma cells (a few)	pos (++)	neg	neg	Trace	Speckled	Lower third	pos (+)
	48	M	Lichenoid (OLP); hd	Lymphocytes	pos (+)	neg	neg	Trace	Speckled	Lower third	neg

(Continues)

TABLE 3 (Continued)

			Histopathological features		DIF analysis						
Authors	**Patients**	**Specimen**	**H&E**	**Inflammatory components**	**IgG**	**IgA**	**IgM**	**C3**	**Pattern**	**Extension**	**Fibrinogen BMZ**
Alshagroud R et al.	49	M	Non-specific	n/a	pos	n/a	n/a	n/a	Speckled	Lower third	n/a
	50	M	n/a	n/a	pos	n/a	n/a	n/a	Speckled	Lower third	n/a
Ko EM et al.	51	M	Lichenoid	Lymphocytes	pos	pos	neg	neg	Speckled	Lower third	pos
	52	M	Lichenoid	Lymphocytes, plasma cells	pos	neg	neg	neg	Speckled	Lower third	pos
	53	M	Lichenoid	Lymphocytes, plasma cells	pos	neg	neg	neg	Speckled	Lower third	neg
	54	M	Lichenoid; hd	Lymphocytes, plasma cells	pos[c]	neg	neg	neg	Speckled	Lower third[d]	pos
	55	M	Lichenoid; hd	Lymphocytes, plasma cells	pos	neg	neg	neg	Speckled	Lower third	neg
Reddy R et al.	56	M	n/a	n/a	pos (+++)	neg	neg	neg	Speckled	Lower third	pos (++)
	57	M	n/a	n/a	pos (++)	neg	neg	Trace	Speckled	Lower third	neg
	58	M	n/a	n/a	pos (+++)	neg	neg	neg	Speckled	Lower third	pos (++)
	59	M	n/a	n/a	pos (+++)	neg	neg	neg	Speckled	Lower third	pos (+++)
	60	M	n/a	n/a	pos	neg	neg	neg	Speckled	Lower third	pos (++)
	61	M	n/a	n/a	pos (+)	neg	neg	neg	speCkled	Lower third	pos (+++)
	62	M	n/a	n/a	pos (++)	neg	neg	neg	Speckled	Lower third	neg
	63	M	n/a	n/a	pos (++)	neg	neg	neg	Speckled	Lower third	pos (+++)
	64	M	n/a	n/a	pos (+++)	neg	neg	pos (++)[a]	Speckled	Lower third	neg
	65	M	n/a	n/a	pos	neg	neg	neg	Speckled	Lower third	pos (++)
	66	M	n/a	n/a	pos (+++)	neg	neg	neg	Speckled	Lower third	neg
	67	M	n/a	n/a	pos (++)	neg	neg	neg	Speckled	Lower third	pos (+++)
	68	M	n/a	n/a	pos	neg	neg	neg	Speckled	Lower third	pos (+++)
	69	M	n/a	n/a	pos (++)	neg	neg	neg	Speckled	Lower third	pos (+)
	70	M	n/a	n/a	pos (++)	neg	neg	neg	Speckled	Lower third	pos (+++)
	71	M	n/a	n/a	pos (++)	neg	neg	neg	Speckled	Lower third	neg
	72	M	n/a	n/a	pos (+++)	neg	neg	neg	Speckled	Lower third	neg
Azzi L et al. (current paper)	73	M (and C)	Lichenoid; hd	Lymphocytes, plasma cells	pos	neg	neg	neg	Speckled	Lower third	np

Note. M: mucosal biopsy; C: cutaneous biopsy; hd: hydropic degeneration; n/a: data not available; np: not performed.

[a]Perivascular deposition. [b]Cutaneous biopsy was performed after several years. [c]IgG deposition was not detected at DIF analysis 3 years before. [d]Full thickness evaluation was limited by tangential sectioning.

Oral biopsy findings have been reported for 38 cases; of these, cutaneous findings were also reported for eight cases, while only cutaneous findings were reported in five cases (Table 3).

Although non-specific chronic mucositis was reported in some cases, lichenoid stomatitis was reported in the majority of oral cases (73.68%); in some of these reports, the authors referred to the lichenoid stomatitis as classic OLP or chronic mucositis with lichenoid features.

An atrophic and/or parakeratinized stratified epithelium, a "band-like" interface of inflammatory cell infiltrate, "saw-tooth" rete ridges, vacuolar degeneration of the basal cell layer with replacement by an eosinophilic coagulum and cytoid bodies have been described in CUS and are features very similar to those of OLP.

Unfortunately, detailed histopathological findings are not available, as studies in the literature have been more focused on immunofluorescence findings.

The only study with in-depth histopathological findings was reported by Qari (Qari et al., 2015). In this study, 10 mucosal biopsies were reviewed, and 60% of them showed the same features of OLP, 20% of them showed chronic inflammation with lichenoid features, and 20% of them showed non-specific chronic mucositis. Moreover, while the "band-like" inflammatory infiltrate, and especially the hydropic degeneration, was observed in all cases, the "saw-tooth" rete ridge pattern was only found in half of the cases (50%), and epithelial variation towards atrophy or hyperkeratosis was observed even less frequently (40%).

However, some microscopic features were found to be of great interest for differentiating CUS from OLP.

In fact, a mixed infiltrate with both T lymphocytes and plasma cells was observed in many of the cases reported by Qari (70%), instead of a pure lymphocytic infiltrate. This finding has also been reported by other authors, including ourselves (Beutner et al., 1991; Fourie et al., 2011; Islam et al., 2007; Jaremko et al., 1990; Ko et al., 2018; Lewis et al., 1996; Lorenzana et al., 2000; Molenda & Kozlowski, 2014; Solomon et al., 2003): plasma cells have been reported in a total of 25 cases (67.57%).

In addition, some lesions showed the classic intense, "band-like" inflammatory infiltrate limited to the superficial lamina propria at the interface with the overlying epithelium, as well as a sharply defined deep edge. However, in a group of other cases, a uniform infiltrate was observed extending into the deeper lamina propria in some areas, producing an irregular or hazy deep edge.

Nevertheless, histological analysis failed to identify any features other than hydropic degeneration of the basal cell layer that were constantly present in every case (Qari et al., 2015).

Both CUS and erosive OLP manifest an immunological reaction with lichenoid features and a "band-like" inflammatory infiltrate. T lymphocytes predominate in OLP, whereas an admixture of T lymphocytes and plasma cells often predominates in CUS. However, overlap of the lymphocytic subset is commonly observed; therefore, subtyping the lymphocytic infiltrate is not a consistently reliable method for distinguishing CUS from OLP.

Overall, it should be noted that many features of other immune disorders can overlap with those reported in CUS and that accurate differential diagnosis is required.

For example, MMP, oral lichenoid drug reaction (OLDR), oral lichenoid contact reaction (OLCR) to amalgam and cinnamon, LP pemphigoides, lupus erythematosus, graft-versus-host disease (GVHD) and linear IgA bullous dermatosis, among others, may show similar histopathological findings, but a detailed description of these findings is beyond the scope of this paper (Müller, 2017).

3.4 | Direct immunofluorescence (DIF)

In the first report of CUS (Jaremko et al., 1990), the four original cases of chronic oral ulcers were characterized by an association with a peculiar ANA, which the authors referred to as "*stratified epithelium-specific antinuclear antibody*" (*SES-ANA*). This was the first description of this association in the literature, and the finding guided Jaremko to define a new pathological entity, "CUS associated with SES-ANA" after its clinical and immunopathological appearance.

Direct immunofluorescence revealed the presence of a speckled pattern of SES-ANA deposition, mainly composed of IgGs, in cells of the basal layer and the bottom three layers of cells. Biopsies were collected from both lesional and non-lesional mucosa, as well as sometimes from the skin.

An independent study (Parodi & Cardo, 1990) of two other patients confirmed these findings, leading the authors to hypothesize that the disease is a type of immune variant of erosive OLP.

From the first reports in 1990, all other papers dealing with CUS have revealed the presence of speckled SES-ANA deposition within the lower third of the epithelium in bioptical specimens, either mucosal or cutaneous.

A total of 62 DIF analyses have been reported (Table 3).

Among them, 60 (96.77%) showed a positive signal with a speckled pattern for SES-ANA IgG autoantibodies within the lower third of the epithelium, with reported variations in signal intensity. DIF yielded a negative result in only two cases, but in the same cases, indirect immunofluorescence showed a positive result (Kapińska-Mrowiecka et al., 2010; Wörle et al., 1997).

Interestingly, one case showed positive results only after 3 years (Ko et al., 2018).

An adjunctive signal for IgA was also observed in seven cases (15.56%), but most studies have not reported whether IgA was analysed. Moreover, the IgA signal determined by DIF is not as intensive as the IgG signal, and to date, no correlations have been found between a positive IgA signal and demographic or clinical features of the disease, as has been described in MMP (Fourie et al., 2011; Jaremko et al., 1990; Qari et al,. 2015; Solomon et al., 2003). Additionally, in some cases, adjunctive IgM (four cases, i.e., 9.30%) and C3 (eight cases, i.e., 18.18%) deposition was observed (Parodi & Cardo, 1990; Qari et al., 2015; Reddy et al., 2018).

Another feature reported for several CUS samples was the deposition of fibrinogen, described as having a pattern similar to that of LP, that is, fluorescence outlining the basement membrane zone (BMZ) with irregular extensions into the superficial lamina propria, yielding a shaggy appearance (Solomon, 2008).

The presence of fibrinogen at the BMZ was highlighted in 27 cases (61.36%), but the pattern was described in only three papers (Church & Schosser, 1992; Ko et al., 2018; Lewis et al., 2006); for the remaining cases, it was unclear whether the fibrinogen deposition was similar to the lichenoid pattern or was non-specific fibrin deposition secondary to inflammation.

Many papers have not mentioned fibrinogen deposits, but it is not clear whether the deposits were absent or the authors did not take this feature into consideration. Thus, further investigation is required to establish whether such fibrinogen deposition can be considered a diagnostic criterion for CUS.

Direct immunofluorescence is considered the gold standard for the diagnosis of CUS. To date, the presence of speckled IgG antibody deposits in the lower third of the epithelium has been described only in CUS and not in any other immunological disease, even though Chorzelski has described positive DIF findings in 4 cases without oral lesions (Chorzelski et al., 1998; Olszewska, Jarząbek-Chorzelska, Kołacińska-Strasz, Blaszczyk, & Jabłońska, 1999). Only in vulvovaginal-gingival-pilar LP (VVG-LP), an in vivo SES-ANA deposition was detected, also in the genital mucosa, but the disease presents with several clinical features different from those of CUS; hence, further research is required to clarify the immunological relationship between CUS and VVG-LP (Olszewska et al., 2016).

However, only certain laboratories are equipped to perform DIF, and sectioning of the oral mucosa requires skilled technical processing, as erroneous orientation of the specimen may result in an inconclusive diagnosis (Solomon, 2008). In addition, it should be considered that less than 1% of specimens processed for DIF reveal CUS; thus, the disease is not a common finding for pathologists (Rinaggio, Crossland, & Zeid, 2007).

Regarding differential diagnosis, DIF findings are indispensable for differentiating CUS from other immunological diseases, such as pemphigus vulgaris, MMP, bullous pemphigoid, LP pemphigoides, linear IgA bullous dermatosis, acquired epidermolysis bullosa, herpetiform dermatitis and lupus erythematosus (Mustafa et al., 2015).

3.5 | Indirect immunofluorescence (IIF)

Since the first reports of CUS, patient serum samples have been analysed by IIF, the distinguishing feature of which is the presence of serum IgG antibodies specifically binding to epithelial nuclei within the basal layer in a speckled pattern. This analysis is positive only on specific epithelial substrates, such as monkey and guinea pig oesophagus, while the total absence and, in some cases, very low antibody titres are detected when IIF is performed on substrates commonly used for other autoimmune disorders, such as HEp-2 cells or monkey kidney. These findings reinforce the name Jaremko gave to these autoantibodies, that is, SES-ANAs.

Indirect immunofluorescence analysis has shown that these autoantibodies are predominantly located in the basal layer of the epithelial substrate, which is quite different from DIF analysis, which also reveals these autoantibodies in suprabasal layers extending through the lower third of the epithelium. This feature suggests the potential continuous in vivo SES-ANA reactions, resulting in the chronic exposure of cells to the autoantibodies (Jaremko et al., 1990).

IIF analysis was reported in thirty-six cases of the 73 cases cited in the literature (49.32%) (Table 4).

Among the classic IIF substrates, HEp-2 cells, which are usually used for detecting ANA in the serum samples of patients with several autoimmune diseases, yielded negative results in 27 cases and positive results in five cases, but with very low titres (Jaremko et al., 1990; Molenda & Kozlowski, 2014; Solomon et al., 2003; Wörle et al., 1997).

The use of mouse kidney (eight cases) and rat liver (two cases) confirmed the useless role of non-epithelial substrates for IIF in CUS. The results for anti-dsDNA, anti-RNP, anti-Sm, anti-Ro and anti-La were also negative.

In contrast, the use of epithelial substrates, such as monkey oesophagus (19 cases) and guinea pig oesophagus (27 cases), almost always resulted in a positive IgG SES-ANA signal. Guinea pig oesophagus appeared as the most sensitive substrate, with an expression of very high antibody titres, usually more than 1:10.240 (12 cases), 1:5.120 (3 cases) and 1:2.560 (5 cases).

Additionally, except for one case in which a correlation between the clinical severity of the disease and the antibody titres was highlighted (Beutner et al., 1991), no correlations between the serum analysis results and the clinical intensity of the disease have been found.

Only one paper reported a negative result at IIF analysis, but it did not describe which substrates were used (Fourie et al., 2011).

Indirect immunofluorescence analysis has been indicated as the gold standard for diagnosing CUS, but several studies, especially those by Parodi (Cacciapuoti et al., 2004; Cozzani et al., 2008; Ebrahimi et al., 2007; Parodi et al., 2007), have noted how serum SES-ANAs could also be detected in 15% of OLP patients, with or without erosive and ulcerated lesions, excluding overlap with CUS because the latter is always associated with an ulcerative clinical appearance.

Moreover, one study demonstrated the presence of SES-ANAs in approximately 70% of patients affected by vulvovaginal-gingival-pilar LP (Olszewska et al., 2016).

Ultimately, positive IIF results may be suggestive, but not conclusive, in diagnosing CUS. In contrast, DIF analysis reveals a specific speckled SES-ANA pattern that has never been described in OLP and represents an exclusive feature.

Based on these considerations, it could be stated that the gold standard for diagnosing CUS is DIF and that IIF may detect false-negative DIF results caused by improper specimen preparation or by a lack of technical skill. Thus, IIF could reinforce the diagnosis or correct the specificity of the direct analysis, but IIF alone is not sufficient for a diagnosis of CUS.

3.6 | Chronic ulcerative stomatitis protein (CUSP) antigen

The nature of the epithelial antigen involved in CUS has been investigated since the first reports in 1990.

TABLE 4 IIF analysis results of CUS patients

Authors	Patients	IIF outcomes	Epithelial substrates			Classic substrates		
			Monkey oesophagus	Guinea pig oesophagus	Human oesophagus	HEp-2	Mouse kidney	Rat liver
Jaremko WM et al.	1	Positive	1:5.120	1:≥10.240	np	neg[a]	neg	np
	2	Positive	1:5.120	1:≥10.240	np	1:40 homog[a]	1:40 homog	np
	3	Positive	1:≥10.240	1:≥10.240	np	neg[a]	neg	np
	4	Positive	1:1.280	1:≥10.240	np	neg[a]	1:20 speckled	np
Parodi AP and Cardo PP	5	Positive	1:5.120	np	np	np	np	neg
	6	Positive	1:10.240 (IgM 1:320)	np	np	np	np	neg
Beutner EH et al.	7	Positive	1:160	np	np	neg[a]	np	np
	8	Positive	n/a	n/a	n/a	n/a	n/a	n/a
(Chorzelski et al., Bańka-Wrona A et al.)	9	Positive	1 ≥ 10.240; (1:5.120)	1:≥10.240; (1:20.480)	1:10.240	neg	np	np
	10	Positive	np	1:≥10.240	np	neg	np	np
Church LF and Schosser RH	11	Positive	1:160	np	np	neg	np	np
Lewis JE et al.	12	Positive	1:80	1:1.280	np	neg	neg	np
Wörle et al.	13	Positive	IgG-IgA 1:40 – 1:320	np	np	IgA-IgM 1:320 – 1:640[b]	np	np
Chorzelski TP et al.	14	Positive	np	1:2.560	1:640	neg	np	np
	15	Positive	np	1:20.180	1:2.560	neg	np	np
	16	Positive	np	1:10.240	1:1.280	neg	np	np
	17	Positive	np	1:10.240	1:5.120	neg	np	np
	18	Positive	np	1:5.120	1:2.560	neg	np	np
	19	Positive	np	1:10.240	1:1.280	neg	np	np
	20	Positive	np	1:2.560	1:1.280	neg	np	np
	21	Positive	np	1:5.120	1:2.560	neg	np	np
	22	Positive	np	1:5.120	1:5.120	neg	np	np
	23	Positive	np	1:2.560	1:640	neg	np	np
	24	Positive	np	1:2.560	1:1.280	neg	np	np
	25	Positive	np	1:2.560	1:160	neg	np	np
	26	Positive	np	1:10.240	1:2.560	neg	np	np
	27	Positive	np	1:10.240	1:2.560	neg	np	np
Lorenzana ER et al.	28	Positive	1:320	np	np	neg	np	np
Solomon LW et al.	29	Positive	≥1:40	≥1:320	np	neg	neg	np
	30	Positive	≥1:1.280	≥1:1.280	np	1:160	1:20	np
	31	Positive	1:20	≥1:320	np	1:160	neg	np

(Continues)

TABLE 4 (Continued)

Authors	Patients	IIF outcomes	Epithelial substrates			Classic substrates		
			Monkey oesophagus	Guinea pig oesophagus	Human oesophagus	HEp-2	Mouse kidney	Rat liver
Islam MN et al.	32	np	np	np	np	np	np	np
	33	np	np	np	np	np	np	np
	34	np	np	np	np	np	np	np
	35	np	np	np	np	np	np	np
Kapińska-Mrowiecka M et al.	36	Positive	1:640	1:1.280	np	np	np	np
Fourie J et al.; Jacyk WK et al.	37	Negative	n/a	n/a	n/a	n/a	n/a	n/a
Molenda I and Kozlowski Z	38	Positive	pos (n/a)	np	np	1:640	np	np
Qari H et al.	39	np	np	np	np	np	np	np
	40	np	np	np	np	np	np	np
	41	np	np	np	np	np	np	np
	42	np	np	np	np	np	np	np
	43	np	np	np	np	np	np	np
	44	np	np	np	np	np	np	np
	45	np	np	np	np	np	np	np
	46	np	np	np	np	np	np	np
	47	np	np	np	np	np	np	np
	48	np	np	np	np	np	np	np
Alshagroud et al.	49	Positive	pos (n/a)	pos (n/a)	n/a	neg	n/a	n/a
	50	Positive	pos (n/a)	pos (n/a)	n/a	neg	n/a	n/a
Ko EM et al.	51	np	np	np	np	n/a	n/a	n/a
	52	np	np	np	np	n/a	n/a	n/a
	53	np	np	np	np	neg	n/a	n/a
	54	np	np	np	np	n/a	n/a	n/a
	55	np	np	np	np	n/a	n/a	n/a

(Continues)

TABLE 4 (Continued)

Authors	Patients	IIF outcomes	Epithelial substrates			Classic substrates		
			Monkey oesophagus	Guinea pig oesophagus	Human oesophagus	HEp-2	Mouse kidney	Rat liver
Reddy R et al.	56	np	np	np	np	np	np	np
	57	np	np	np	np	np	np	np
	58	np	np	np	np	np	np	np
	59	np	np	np	np	np	np	np
	60	np	np	np	np	np	np	np
	61	np	np	np	np	np	np	np
	62	np	np	np	np	np	np	np
	63	np	np	np	np	np	np	np
	64	np	np	np	np	np	np	np
	65	np	np	np	np	np	np	np
	66	np	np	np	np	np	np	np
	67	np	np	np	np	np	np	np
	68	np	np	np	np	np	np	np
	69	np	np	np	np	np	np	np
	70	np	np	np	np	np	np	np
	71	np	np	np	np	np	np	np
	72	np	np	np	np	np	np	np
Azzi L et al. (current paper)	73	np	np	np	np	np	np	np

Note. n/a; data not available; np: not performed.

[a]Negative results also for anti-dsDNA, anti-RNP, anti-Sm, anti-Ro, anti-La. [b]Positive results also on other substrates and gluteal skin.

In 1990 and 1998, Parodi performed an in-depth analysis of serum from 7 CUS patients and found that circulating antibodies were directed against an antigen present in the epithelial cells of several mammalian species. The data showed that the antigen is probably a multimolecular 70-kDa DNA–protein (non-histone) complex not expressed in non-epithelial substrates (Parodi & Cardo, 1990; Parodi, Cozzani, Chorzelski, Beutner, & Rebora, 1998).

The identification of the autoantigen in CUS, that is, CUSP, was made by comparing nine serum samples from CUS patients with samples from patients with recurrent aphthous stomatitis, OLP, dermatomyositis, and lupus erythematosus, as well as healthy patients (Lee et al., 1999). The 70-kDa epithelial nuclear protein was the major autoantigen in the CUS sera. Sequencing of the cDNA for this protein revealed CUSP to be homologous to both the p53 tumour suppressor and the p73 putative tumour suppressor and to be a splicing variant of the rat KET gene.

In addition, Parodi confirmed the antibodies that precipitate the 70-kDa molecule, as a member of the p53 family, to be the same as those that bind the nuclei of epithelial cells (Parodi, Cozzani, Cacciapuoti, & Rebora, 2000).

TP53 is a tumour suppressor gene that is mutated in more than 50% of human tumours. Until 1997, p53 was thought to be a unique protein; then, two new family members were identified and named p73 and rat KET genes. Other homologues of KET have since been reported as splice variants of the same gene: p51A, p51B, p40, p73L and p63 (Schmale & Bamberger, 1997).

The p63 gene is located on chromosome 3q27-29 and encodes six proteins with homology to p53 (Yang et al., 1998). In fact, the structure of the different p63 proteins is similar to that of p53, with an N-terminal transactivation domain, a central DNA-binding domain and an oligomerization domain close to the C-terminus (Ebrahimi et al., 2007). The three full-length proteins (TAp63α, TAp63β and TAp63γ) contain a transactivation domain in the N-terminus, whereas the other three proteins lack the N-terminal transactivation domain and are restricted to the epithelium (ΔNp63α, ΔNp63β and ΔNp63γ).

The CUSP antigen is an approximately 70-kDa protein with a cDNA sequence identical to that of ΔNp63α, a p63 isoform predominantly expressed in the nuclei of basal cells in the progenitor cell compartment of the stratified epithelium. There, it plays a critical role in the maintenance of epithelium integrity and homeostasis (Dellavalle et al., 2001).

However, some contradictory data have emerged in the literature on CUSP/p63 expression due to the complex array of isoforms encoded by the gene and the specificity of the probes and antibodies utilized.

Moreover, Parodi herself demonstrated that 7% of OLP patients have circulating antibodies directed against the CUSP antigen with different clinical presentations, including non-erosive forms; thus, while SES-ANAs directed against the 70-kDa antigen are always present in CUS, they are not exclusive to this disease (Cacciapuoti et al., 2004).

An original contribution to literature was provided by Prof Lynn Solomon in 2007. She characterized the autoimmune response in 21 CUS serum samples using immunoblotting and immunoprecipitation and found that CUS patients had IgG antibodies against the ΔNp63α antigen. Surprisingly, 52% of the patients also had circulating IgA isotype antibodies. The N-terminal and DNA-binding domains were the immunodominant regions, and cross-reactivity with p53, other p63 isoforms and p73 was limited. Future studies to determine whether CUS patients with circulating IgA antibodies have clinically more severe disease, such as in MMP, would be useful, even though the hypothesis is not yet supported by data (Solomon, Neiders, Zwick, Kirkwood, & Kumar, 2007).

Solomon believed that qualitative techniques used by other authors to determine the recognition of the 70-kDa keratinocyte protein in some LP sera were imprecise and that after the ΔNp63α antigen was cloned, quantitative biomechanical methods would be more likely to provide answers regarding the relationship between CUS and LP.

In addition, to date, only symptomatic cases of CUS with oral ulcerations have been examined by DIF, and DIF has not been applied in asymptomatic cases of non-erosive lichenoid disease that may also have antibodies against ΔNp63α. Only four patients without oral lesions reported by Chorzelski showed positive DIF results: however, it is unclear whether these patients were previously symptomatic or whether they did not show any sign of the disease.

Consequently, Solomon provided a novel, reliable diagnostic assessment for distinguishing CUS from other ulcerative diseases: ELISA for IgG antibodies in CUS sera. A recombinant peptide was produced by the portion of the ΔNp63α N-terminal and DNA-binding domains that was the most immunogenic. This test could be useful for establishing not only the incidence rate of CUS among other oral autoimmune diseases, but also its relationship with OLP (Solomon, Stark, Winter, Kumar, & Sinha, 2010).

Since 2010, no adjunctive studies have been published on the utilization of ELISA for IgG antibodies in CUS patients. However, the method could enable the early detection of CUS in cases with lesions resembling those of erosive OLP exhibiting low response to corticosteroids or in cases of isolated desquamative gingivitis. This method could also be used as a less expensive alternative to IIF for assessing false-negative DIF results.

It is unclear whether the development of hyperactive IgG autoantibodies against ΔNp63α is the primary pathogenic event in CUS or whether the autoimmune response is driven by physiological IgG antibodies responding to ΔNp63α overexpression, secondary to T cell-induced damage to the basal cell layer of the epithelium and to an increase in pro-apoptotic processes. If the increased levels of ΔNp63α exceed the critical threshold of immune tolerance, then a B cell-mediated humoral autoimmune response may supervene (Feller, Khammissa, & Lemmer, 2017).

The disrupted ΔNp63α activity may end in epithelial breakdown with poor healing manifesting clinically as non-healing ulcers and erosions, as suggested by a three-dimensional in vitro study of CUS reporting reduced expression levels of α6β4 integrins and

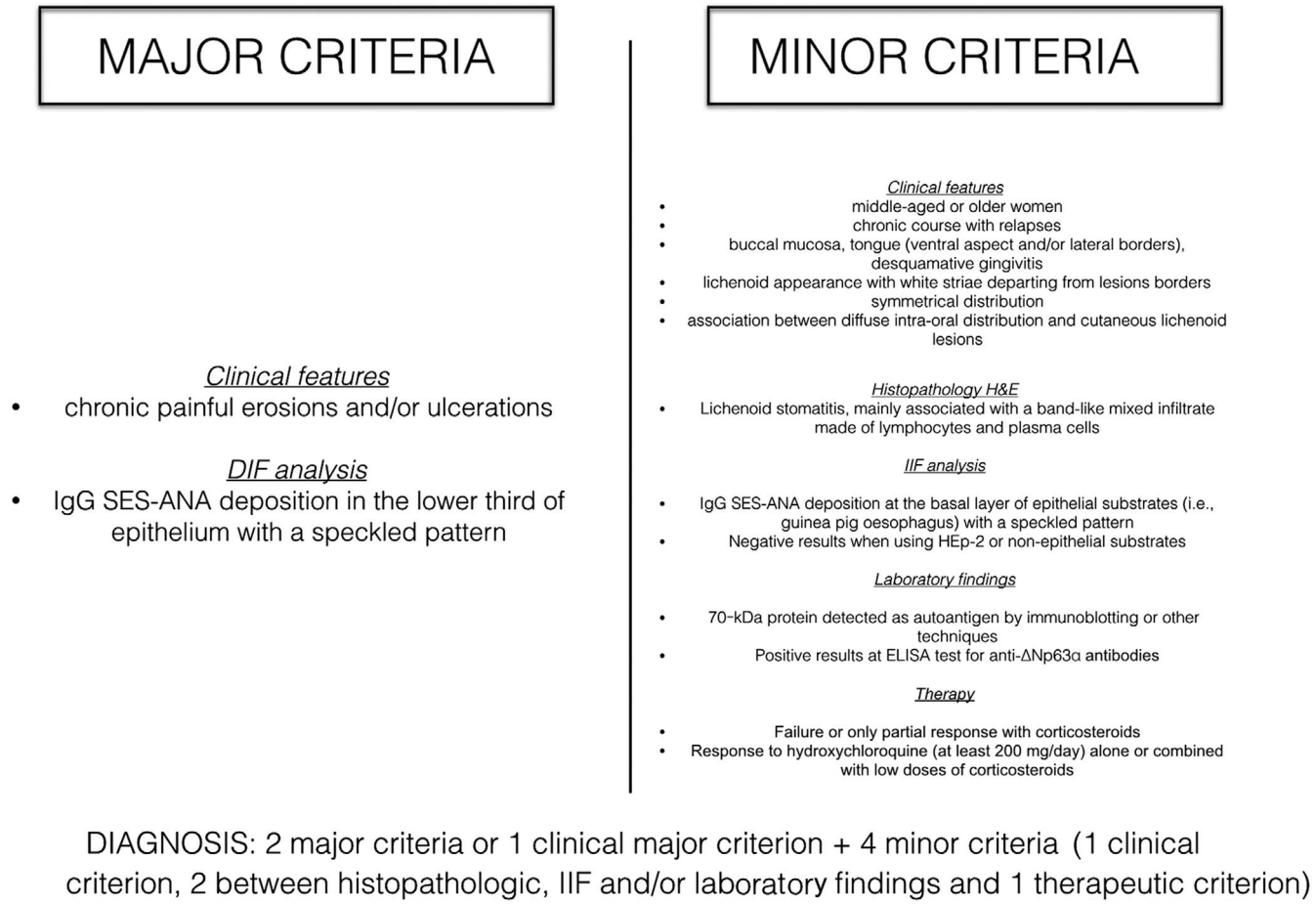

FIGURE 7 Updated diagnostic criteria for CUS

hemidesmosome components after disruption of the basement membrane interface (Carlson, Garlick, & Solomon, 2011).

3.7 | Diagnosis

The diagnostic process for CUS requires intensive collaboration between the oral clinician, the dermatologist and the pathologist.

We have revised the diagnostic criteria originally proposed by Jaremko, Beutner and Chorzelski (Beutner et al., 1991; Chorzelski et al., 1998; Jaremko et al., 1990; Figure 7).

The presence of chronic oral erosions and/or ulcerations is considered the main major criterion for suspecting CUS. This criterion will probably be revised when the ELISA technique proposed by Solomon (Solomon et al., 2010) can be used to detect CUS before clinical manifestation, at earlier stages of the disease, or when only cutaneous involvement is present. To date, the diagnosis of CUS cannot be formulated without oral involvement in the form of erosions and ulcers.

The typical speckled IgG SES-ANA deposition in the lower third of the epithelium detected by DIF analysis is considered the gold standard for confirming CUS. Although Chorzelski reported four patients with positive DIF results and without oral erosions (Chorzelski et al., 1998), it could be stated that the simultaneous presence of these two major criteria is highly suggestive of CUS.

In contrast, when DIF analysis is not performed well or is unavailable, the clinical major criterion should be accompanied by four other minor criteria for the diagnosis of CUS.

Minor criteria are described as clinical, histopathological, laboratory and therapeutic features of the disease that have been reported in the international literature but are not in all CUS cases.

Finally, a combination of the clinical major criterion (i.e., chronic erosions and ulcers) with one clinical minor criterion, two among histopathological, IIF and/or laboratory findings and one therapeutic minor criterion can compensate for the absence of DIF analysis.

It is imperative that DIF analysis is conducted by an expert pathologist; otherwise, if available, IIF or ELISA could be used to assess the presence of false-negative DIF results due to imprecision or technical bias.

Finally, it should be highlighted that a poor or low response to corticosteroid therapy has been described as a distinguishing feature of CUS, as well as a good response to hydroxychloroquine, but as these findings have not been reported in all cases, they cannot be considered major criteria.

3.8 | Therapy

As in many oral immunopathogenic diseases, the objective of treatment in CUS patients is to relieve symptoms, prevent secondary

TABLE 5 Therapeutic outcomes of CUS patients

		Corticosteroid therapy		Antimalarial therapy				Notes
Authors	Patients	Only corticosteroids	Outcomes	Drug	Dosage	Combination	Outcomes	Adjunctive info
Jaremko WM et al.	1	No	//	Hydroxychloroquine	200 mg/day	Topical fluocinolone	Success	Originally diagnoses as lupus erythematosus
	2	Prednisone (60 mg/day)	Unsuccess	Hydroxychloroquine	200 mg/day	No	Success	
	3	n/a	n/a	n/a	n/a	n/a	n/a	
	4	Topical fluocinonide	Success	No	//	//	//	Topical tetracyclines and diphenhydramine (twice/day)
Parodi AP and Cardo PP	5	n/a	n/a	n/a	n/a	n/a	n/a	
	6	n/a	n/a	n/a	n/a	n/a	n/a	
Beutner EH et al.	7	Topical betamethasone	Partial success	No	//	//	//	
	8	No	//	Hydroxychloroquine	200 mg/day	No	Success	Antimalarial prophylaxis during African journey; GI side effects
(Chorzelski et al., Bańka-Wrona A et al.)	9	Topical corticosteroids	Unsuccess	Hydroxychl (chloroq)	200 mg/day	Prednisone	Success	Relapse with skin LP after 18 years; follow-up period of 20 years; failure with sulphons
	10	Topical clobetasol	Success	No	//	//	//	
Church LF and Schosser RH	11	Topical dexamethasone 0.5 mg/5 ml	Partial success	No	//	//	//	
Lewis JE et al.	12	No	//	Hydroxychloroquine	200 mg/day	No	Success	2.5 years follow-up
Wörle et al.	13	Systemic prednisolone (40–100 mg)	Unsuccess	Hydroxychloroquine	400 mg/day (200)	No	Success	Topical tetracyclines, local anaesthetics and dapsone (50 mg/day) with unsuccess
Chorzelski TP et al.	14	No	//	Chloroquine	Not reported	Prednisone	Success	
	15	No	//	Chloroquine	Not reported	Prednisone	Partial success	Prednisone and dapsone success
	16	No	//	Chloroquine	Not reported	Prednisone	Success	
	17	No	//	Chloroquine	Not reported	Prednisone	Success	
	18	No	//	Chloroquine	Not reported	Prednisone	Partial success	Gluten-free diet success
	19	No	//	Chloroquine	Not reported	No	Unsuccess	Prednisone and dapsone success
	20	No	//	Chloroquine	Not reported	Prednisone	Success	
	21	No	//	Chloroquine	Not reported	No	Success	
	22	No	//	Chloroquine	Not reported	Prednisone	Success	
	23	No	//	Chloroquine	Not reported	Prednisone	Success	Liver side effects
	24	No	//	Chloroquine	Not reported	Prednisone	Success	
	25	No	//	Chloroquine	Not reported	No	Success	
	26	No	//	Chloroquine	Not reported	No	Success	Short follow-up
	27	No	//	Chloroquine	Not reported	Prednisone	Success	

(Continues)

TABLE 5 (Continued)

		Corticosteroid therapy		Antimalarial therapy				Notes
Authors	Patients	Only corticosteroids	Outcomes	Drug	Dosage	Combination	Outcomes	Adjunctive info
Lorenzana ER et al.	28	Topical betamethasone (fluocinonide previously)	Success	No	//	//	//	Sjögren syndrome
Solomon LW et al.	29	No	//	No	//	//	//	Reduction in psychological distress and improvement
	30	Topical clobetasol	Unsuccess	Hydroxychloroquine	200 mg/day	No	Partial success	
	31	n/a	n/a	n/a	n/a	n/a	n/a	No follow-up
Islam MN et al.	32	Topical fluocinonide	Unsuccess	Hydroxychloroquine	400 mg/day	No	Success	
	33	Topical fluocinonide +dexamethasone 0.5 mg/5 ml	Unsuccess	Hydroxychloroquine	800 mg/day	No	Success	6-month follow-up
	34	No	//	Hydroxychloroquine	200 mg/day	Prednisone	Success	Sjögren syndrome
	35	No	//	Hydroxychloroquine	200 mg/day	n/a	n/a	No follow-up
Kapińska-Mrowiecka M et al.	36	Topical corticosteroids	Unsuccess	Hydroxychloroquine	400 mg/day (200)	Methylpr 16 mg (4)	Success	Topical 0.1% tacrolimus ointment; follow-up of 4 years; persisting pseudopelade
Fourie J et al.; Jacyk WK et al.	37	No	//	Chloroquine	200 mg/day	No	Success	Cyclosporine (skin lesion) 200 mg/day; topical 1% pimecrolimus ointment (skin)
Molenda I and Kozlowski Z	38	Systemic methylpredni-solone 16 mg/day	Unsuccess	Chloroquine	500 mg/day (250)	No	Partial success	Topical tacrolimus ointment;systemic cyclosporine (tongue lesions)
Qari H et al.	39	n/a	n/a	n/a	n/a	n/a	n/a	
	40	n/a	n/a	n/a	n/a	n/a	n/a	
	41	n/a	n/a	n/a	n/a	n/a	n/a	
	42	n/a	n/a	n/a	n/a	n/a	n/a	
	43	n/a	n/a	n/a	n/a	n/a	n/a	
	44	n/a	n/a	n/a	n/a	n/a	n/a	
	45	n/a	n/a	n/a	n/a	n/a	n/a	
	46	n/a	n/a	n/a	n/a	n/a	n/a	
	47	n/a	n/a	n/a	n/a	n/a	n/a	
	48	n/a	n/a	n/a	n/a	n/a	n/a	
Alshagroud R et al.	49	n/a	n/a	n/a	n/a	n/a	n/a	
	50	n/a	n/a	n/a	n/a	n/a	n/a	

(Continues)

TABLE 5 (Continued)

		Corticosteroid therapy		Antimalarial therapy				Notes
Authors	Patients	Only corticosteroids	Outcomes	Drug	Dosage	Combination	Outcomes	Adjunctive info
Ko EM et al.	51	n/a	n/a	n/a	n/a	n/a	n/a	
	52	n/a	n/a	n/a	n/a	n/a	n/a	
	53	Topical clobetasol and prednisone	Partial success	Hydroxychloroquine	n/a	n/a	n/a	
	54	Topical corticosteroids	Unsuccess	n/a	n/a	n/a	n/a	
	55	n/a	n/a	n/a	n/a	n/a	n/a	
Reddy R et al.	56	n/a	n/a	n/a	n/a	n/a	n/a	
	57	n/a	n/a	n/a	n/a	n/a	n/a	
	58	n/a	n/a	n/a	n/a	n/a	n/a	
	59	n/a	n/a	n/a	n/a	n/a	n/a	
	60	n/a	n/a	n/a	n/a	n/a	n/a	
	61	n/a	n/a	n/a	n/a	n/a	n/a	
	62	n/a	n/a	n/a	n/a	n/a	n/a	
	63	n/a	n/a	n/a	n/a	n/a	n/a	
	64	n/a	n/a	n/a	n/a	n/a	n/a	
	65	n/a	n/a	n/a	n/a	n/a	n/a	
	66	n/a	n/a	n/a	n/a	n/a	n/a	
	67	n/a	n/a	n/a	n/a	n/a	n/a	
	68	n/a	n/a	n/a	n/a	n/a	n/a	
	69	n/a	n/a	n/a	n/a	n/a	n/a	
	70	n/a	n/a	n/a	n/a	n/a	n/a	
	71	n/a	n/a	n/a	n/a	n/a	n/a	
	72	n/a	n/a	n/a	n/a	n/a	n/a	
Azzi L et al. (current paper)	73	Topical clob/triamc systemic betamet/prednis	Unsuccess	Hydroxychloroquine	400 mg/day (200)	Topical clobetasol	Success	Systemic azathioprine and methotrexate unsuccess

Note. n/a: data not available.

infection, promote healing and prolong periods of remission, even though there is no cure. Information about therapy is available from 37 cases described in the literature (Table 5).

In some anecdotes, patients reportedly experienced the spontaneous remission of symptoms with psychological stress reduction or after adopting a gluten-free diet (Chorzelski et al., 1998).

However, the most troublesome feature of the disease is that CUS does not respond to corticosteroids as favourably as do other immune-mediated diseases (Solomon, 2008). In addition, a variety of topical and systemic corticosteroids, such as fluocinonide, betamethasone, clobetasol, dexamethasone, methylprednisolone and prednisone, have been tested for treating CUS.

Sixteen patients underwent treatment with corticosteroids, which were mainly applied topically and sometimes administered systemically, but the majority (81.25%) of patients showed no or only partial remission, almost always followed by frequent relapses after treatment interruption.

In three cases, dapsone was prescribed associated with corticosteroids, resulting in two cases with improvement (Chorzelski et al., 1998) and in one failure due to side effects (Wörle et al., 1997). Topical tetracyclines were also prescribed in two cases, but with no evidence to support their usage (Jaremko et al., 1990; Wörle et al., 1997).

Nevertheless, a very interesting feature of CUS is that it seems to respond to antimalarials.

Jaremko was the first to describe remission in a patient who was erroneously diagnosed with lupus erythematosus (Jaremko et al., 1990). Another patient showed unexpected improvement after taking antimalarials to prevent infectious disease during a journey in Africa (Beutner et al., 1991).

Since then, many authors have reported successful outcomes after treatment with hydroxychloroquine or related drugs (Beutner et al., 1991; Chorzelski et al., 1998; Fourie et al., 2011; Islam et al., 2007; Jaremko et al., 1990; Kapińska-Mrowiecka et al., 2010; Lewis et al., 1996; Molenda & Kozlowski, 2014; Solomon et al., 2003; Wörle et al., 1997).

Thirty cases described in the literature were managed with antimalarials. Among these patients, 15 were treated with the antimalarial agent alone, resulting in 10 successful outcomes, two partial remissions and one failure, while two patients were lost to follow-up; in other 15 cases, mainly reported by Chorzelski (Chorzelski et al., 1998), full success was achieved by combined treatment with chloroquine and corticosteroids, mainly prednisone, with complete clearing of the oral lesions in 13 patients and partial remission in two patients.

While hydroxychloroquine doses as low as 200 mg/day may induce improvement and, in some cases, the complete clearing of oral lesions, some authors have also described the use of higher doses compared with those used in other studies, such as 400 mg/day, as in our case report (Islam et al., 2007; Kapińska-Mrowiecka et al., 2010; Wörle et al., 1997), or 800 mg/day (Islam et al., 2007).

Hydroxychloroquine interferes with the antigen-processing mechanisms of macrophages and other antigen-presenting cells, resulting in downregulation of the immune response against antigenic peptides (Solomon, 2008). It is often administered to treat lupus erythematosus or prevent GVHD.

Side effects may arise, such as irreversible retinopathy, toxic psychosis, neuromyopathy, agranulocytosis and aplastic anaemia.

Therefore, the close follow-up of patients being treated with hydroxychloroquine is warranted (Solomon, 2008).

Almost all papers report a follow-up period of only a few months, during which patients usually remained asymptomatic or showed occasional relapses. These slight relapses were usually treated with topical or systemic corticosteroids in adjunction to antimalarials. The same protocol was carried out in our clinical case, with a follow-up period of 12 months. However, a paper reported a case with a long-term follow-up, that is, 18 years (Bańka-Wrona et al., 2009). During this period, the patient was asymptomatic and underwent chronic therapy with low doses of prednisone and hydroxychloroquine without any significant relapse. The patient experienced a serious relapse only after 18 years with cutaneous LP lesions and an ulceration on her foot with histopathological features of LP and SES-ANA in vivo binding in the skin.

Another paper described a follow-up period of 4 years, during which hydroxychloroquine or methylprednisolone alone proved unable to clear the lesions, while in contrast their combination resulted in dramatic improvement (Kapińska-Mrowiecka et al., 2010).

It can be affirmed, therefore, that the therapeutic protocol of CUS consists of a combination of low doses of both antimalarial and corticosteroid drugs for a prolonged time.

4 | DISCUSSION

Chronic ulcerative stomatitis is a rare mucocutaneous disorder that was first described by Jaremko and Parodi (Jaremko et al., 1990; Parodi & Cardo, 1990). CUS mainly affects middle-aged and older women by manifesting as chronic ulcerations in the mouth that are usually refractory to conventional treatments with corticosteroids (Qari et al., 2015).

Many times, the presence of white striae around the ulcerations results in clinical overlap with erosive OLP, which is usually responsive to corticosteroids (Solomon, 2008).

The most frequently involved sites are the buccal mucosa, the gingiva and the tongue. Gingival lesions manifest in the form of desquamative gingivitis, which is very similar to the clinical appearance of erosive OLP or vesiculobullous diseases (Solomon et al., 2003). The lesions are usually ulcerative and not preceded by bullae or vesicles, even though a positive Nikolsky's sign has been reported in nine cases in the literature (Beutner et al., 1991; Chorzelski et al., 1998; Ko et al., 2018; Reddy et al., 2018; Wörle et al., 1997).

Despite the term CUS, the skin is involved in 22.5% of cases, with either non-specific or lichenoid lesions, the latter of which are associated with a more diffuse intraoral involvement. It is interesting to note that in several cases, including the case reported here, the skin may be involved several years before or after the mouth; thus, the term CUS may be inadequate for describing this pathological entity.

H&E histopathological findings in CUS are non-specific, although some features may raise suspicion in pathologists, such as the presence of lichenoid stomatitis with a superficial mixed inflammatory infiltrate mainly composed of lymphocytes and plasma cells or the absence of complete dermo-epithelial clefting (Qari et al., 2015). However, these findings are not conclusive, and the only way to form a diagnosis is by DIF analysis, where IgG antibody deposition in the nuclei of cells in the lower third of the epithelium is commonly observed, and this deposition is considered a distinguishing feature of the disease (Jaremko et al., 1990). Occasionally, IgA signal and fibrinogen deposits at the BMZ may also be found (Solomon, 2008), but their role in CUS remains to be determined.

The same pattern has been described by IIF analysis (Jaremko et al., 1990; Parodi & Cardo, 1990), but only on specific epithelial substrates, such as guinea pig and monkey oesophagus; on other common substrates, such as HEp-2 cells and mouse kidney, the results are negative. This particular feature led the first authors to describe the disease to name the IgG antibodies in CUS SES-ANAs (Jaremko et al., 1990).

A group of researchers identified a 70-kDa antigen involved in CUS, ΔNp63α, which is a specific epithelial p63 isoform involved in the maturation of epithelial tissues in mammals (Lee et al., 1999; Parodi & Cardo, 1990; Parodi et al., 2000, 1998). Although ΔNp63α, known as CUSP, is the CUS antigen, some authors have reported the same findings in erosive and non-erosive OLP (Cacciapuoti et al., 2004; Cozzani et al., 2008; Parodi et al., 2007), especially in vulvo-vaginal-gingival-pilar LP (Olszewska et al., 2016). Thus, IIF analysis alone is not conclusive for the diagnosis of CUS, while the DIF findings have been associated only with CUS and not with OLP, to date. The only exception in which SES-ANA in vivo binding was detected is in VVG-LP, whose clinical features, however, are different from those of CUS (Olszewska et al., 2016).

These confounding findings raise the question of whether CUS is a distinct entity or a variant of erosive OLP. Some authors believe that CUS is a hyper-reactive form of OLP in which, after T lymphocytes induce cytotoxic damage within the basal cells of the epithelium, a B cell-mediated reaction occurs against the exposed CUSP antigen (Carlson et al., 2011). In a recent paper, indeed, plasma cells were noted in association with ulceration, subepithelial clefting, or scarring (Ko et al., 2018).

However, whether CUS is a variant of OLP or a distinct entity, it should be considered that SES-ANAs have not yet been described in OLP by DIF analysis and that the most clinically important identifying feature of CUS is the lack of a response to conventional treatment with corticosteroids, a troublesome feature for both the clinician and the patient (Solomon, 2008).

Thus, diagnosis requires the simultaneous presence of chronic oral ulcerations and positive DIF results for SES-ANAs in the lower third of the epithelium.

If DIF analysis is unavailable, a combination of clinical features, histopathological, IIF and laboratory findings and therapeutic outcomes may increase the suspicion of CUS in the stomatologist, as we have proposed in this paper through updated diagnostic criteria.

However, the clinician should be aware that if histologically confirmed erosive OLP does not respond to corticosteroids, DIF should be performed to confirm or exclude CUS, thus avoiding a delayed diagnosis, which is very common in CUS patients.

Finally, CUS responds better to antimalarials, especially hydroxychloroquine, at doses of 200 mg/day or higher, alone or in combination with corticosteroids to avoid relapses and improve patient quality of life (Bańka-Wrona et al., 2009; Beutner et al., 1991; Chorzelski et al., 1998; Fourie et al., 2011; Islam et al., 2007; Jaremko et al., 1990; Kapińska-Mrowiecka et al., 2010; Lewis et al., 1996; Molenda & Kozlowski, 2014; Solomon et al., 2003; Wörle et al., 1997).

In future, the relationship between OLP and CUS should be further examined by both DIF and the ELISA method introduced by Solomon not only to identify the reaction against ΔNp63α even with false-negative DIF results, but also to detect the disease during its oral early stages or when confined to the skin (Solomon et al., 2010).

Based on the considerations described in this review, the term CUS appears inadequate for describing the disease and should be changed.

For example, the term ***Chronic ulcerative disorder with SES-ANA*** (*CUD*) could be more adequate. In this context, it may be defined as *oral CUD* and/or *cutaneous CUD*, similarly to the well-established distinction between OLP and LP. In addition, a new research field could be created when cutaneous LP showing positive DIF results for SES-ANAs is not associated with oral lesions (Chorzelski et al., 1998) or in the peculiar context of VVG-LP, whose relation with CUD has to be further investigated.

ACKNOWLEDGEMENTS

We are immensely grateful to Prof. Malgorzata Olszewska who provided an important contribution to our paper. Prof May Chan kindly helped us in adding recently published cases to the review. Prof Angelo Tagliabue is the elected Rector of the University of Insubria (2018-2024). Prof Marina Tettamanti supervised the revision process in the English language. Dr Fabio Croveri is a PhD student of "Life Sciences and Biotechnology" course at University of Insubria. Dr Maria Pellilli is a student of the Anatomical Pathology postgraduate programme, Department of Medicine and Surgery, University of Insubria, Varese, Italy. Supervisor: Prof Fausto Sessa. The case report showed in this paper was presented at the poster session of the 14th Biennial Congress of European Association of Oral Medicine, 27th September to 29th September, Gothenburg, Sweden.

CONFLICT OF INTERESTS

None to declare.

AUTHOR CONTRIBUTIONS

Lorenzo Azzi is the corresponding author and managed the clinical case and the CUS review. Michele Cerati and Maria Pellilli provided histopathological slides and images along with description. Maurizio Lombardo managed the dermatologic aspects of the clinical case. Fabio Croveri and Vittorio Maurino are part of the oral pathology team at our dental hospital and helped in literature review

and analysis. Prof Angelo Tagliabue is Dean of the Department of Medicine and Surgery, University of Insubria, and recently he has been elected rector of University of Insubria. Prof Lucia Tettamanti is head of the Research centre in rare diseases of the oral cavity and maxillofacial region. Prof Malgorzata Olszewska is the revisor author and helped in organizing the case series reported in tables. Moreover, her precious contribution helped us to access to the Polish literature in which several cases were described.

ORCID

Lorenzo Azzi https://orcid.org/0000-0003-2532-7651
Vittorio Maurino https://orcid.org/0000-0002-7386-4956
Angelo Tagliabue https://orcid.org/0000-0002-4233-8427
Lucia Tettamanti https://orcid.org/0000-0003-1558-5729
Malgorzata Olszewska https://orcid.org/0000-0002-2744-8353

REFERENCES

Alshagroud, R., Neiders, M., Kramer, J. M., & Suresh, L. (2017). Clinicopathologic significance of in vivo antinuclear autoantibodies in oral mucosal biopsies. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*, *124*, 475–482. https://doi.org/10.1016/j.oooo.2017.08.008

Bańka-Wrona, A., Kolacińska-Strasz, Z., Labęcka, H., Kraińska, T., & Olszewska, M. (2009). Przewlekle wrzodziejące zapalenie jamy ustnej. Związek z liszajem płaskim. *Przegląd Dermatologiczny*, *96*, 400–405.

Beutner, E. H., Chorzelski, T. P., Parodi, A., Schosser, R., Guin, J., Cardo, P. P., … Kumar, V. (1991). Ten cases of chronic ulcerative stomatitis with stratified epithelium-specific antinuclear antibody. *Journal of the American Academy of Dermatology*, *24*, 781–782. https://doi.org/10.1016/S0190-9622(08)80367-2

Cacciapuoti, M., Di Marco, E., Cozzani, E., Zerega, B., Descalzi Cancedda, F., & Parodi, A. (2004). The antibody to the 70-kd antigen in chronic ulcerative stomatitis and lichen planus. *Journal of the American Academy of Dermatology*, *50*, 486. https://doi.org/10.1016/S0190-9622(03)02093-0

Carlson, M. W., Garlick, J. A., & Solomon, L. W. (2011). Chronic ulcerative stomatitis: Evidence of autoimmune pathogenesis. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics*, *111*, 742–748. https://doi.org/10.1016/j.tripleo.2010.12.020

Chorzelski, T. P., Olszewska, M., Jarząbek-Chorzelska, M., & Jablońska, S. (1998). Is chronic ulcerative stomatitis an entity? Clinical and immunological findings in 18 cases. *European Journal of Dermatology*, *8*, 261–265.

Chorzelski, T. P. (1990). Chronic ulcerative stomatitis (CUS): Nowa jednostka chorobowa ze swoistym markerem immunologicznym (SESANA). *Przegląd Dermatologiczny*, *77*, 229–234.

Church, L. F. Jr, & Schosser, R. H. (1992). Chronic ulcerative stomatitis associated with stratified epithelial specific antinuclear antibodies. A case report of a newly described disease entity. *Oral Surgery, Oral Medicine, Oral Pathology*, *73*, 579–582.

Cozzani, E., Cacciapuoti, M., Di Marco, E., Zerega, B., Descalzi Cancedda, F., & Parodi, A. (2008). Patients with oral erosive and cutaneous lichen planus may have antibodies directed against the chronic ulcerative stomatitis protein antigen of 70-kDa. *Acta Dermatovenerologica Alpina, Panonica, Et Adriatica*, *17*, 120–124.

Dellavalle, R. P., Egbert, T. B., Marchbank, A., Su, L. J., Lee, L. A., & Walsh, P. (2001). CUSP/p63 expression in rat and human tissues. *Journal of Dermatological Science*, *27*, 82–87. https://doi.org/10.1016/S0923-1811(01)00105-0

Ebrahimi, M., Wahlin, Y. B., Coates, P. J., Wiik, A., Roos, G., & Nylander, K. (2007). Detection of antibodies against p63 and p73 isoforms in sera from patients diagnosed with oral lichen planus. *Journal of Oral Pathology and Medicine*, *36*, 93–98. https://doi.org/10.1111/j.1600-0714.2007.00504.x

Feller, L., Khammissa, R. A. G., & Lemmer, J. (2017). Is chronic ulcerative stomatitis a variant of lichen planus, or a distinct disease? *Journal of Oral Pathology and Medicine*, *46*, 859–863. https://doi.org/10.1111/jop.12561

Fourie, J., van Heerden, W. F., McEachen, S. C., & van Zyl, A. (2011). Chronic ulcerative stomatitis: A distinct clinical entity? *SADJ*, *66*, 119–121.

Glickman, I., & Smulow, J. B. (1964). Chronic desquamative gingivitis: Its nature and treatment. *Journal of Periodontology*, *35*, 397. https://doi.org/10.1902/jop.1964.35.5.397

Islam, M. N., Cohen, D. M., Ojha, J., Stewart, C. M., Katz, J., & Bhattacharyya, I. (2007). Chronic ulcerative stomatitis: Diagnostic management challenges – Four new cases and review of literature. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics*, *104*, 194–203.

Jacyk, W. K., Fourie, J., & van Heerden, W. F. (2012). Chronic ulcerative stomatitis and lichen planus: Just a coincidence or a direct link between the two diseases? *Dermatologia Kliniczna*, *14*, 127–129.

Jaremko, W. M., Beutner, E. H., Kumar, V., Kipping, H., Condry, P., Zeid, M. Y., … Chorzelski, T. P. (1990). Chronic ulcerative stomatitis associated with a specific immunological marker. *Journal of the American Academy of Dermatology*, *22*, 215–220.

Kapińska-Mrowiecka, M., Czubak-Macugowska, M., Michcik, A., Chomik, P., & Wlodarkiewicz, A. (2010). Chronic ulcerative stomatitis (CUS). Lichen planus disseminatus, unguium pedis utriusque and pseudopelade. *American Journal of Case Reports*, *11*, 222–227.

Ko, E. M., Danciu, T. E., Fullen, D. R., & Chan, M. P. (2018). Chronic ulcerative stomatitis: Case series of an under-recognized entity. *Journal of Cutaneous Pathology*, *45*, 927–932. https://doi.org/10.1111/cup.13347

Lee, L. A., Walsh, P., Prater, C. A., Su, L. J., Marchbank, A., Egbert, T. B., … Jablońska, S. (1999). Characterization of an autoantigen associated with chronic ulcerative stomatitis: The CUSP autoantigen is a member of the p53 family. *The Journal of Investigative Dermatology*, *113*, 146–151.

Lewis, J. E., Beutner, E. H., Rostami, R., & Chorzelski, T. P. (1996). Chronic ulcerative stomatitis with stratified epithelium-specific antinuclear antibodies. *International Journal of Dermatology*, *35*, 272–275.

Lorenzana, E. R., Rees, T. D., Glass, M., & Detweiler, J. G. (2000). Chronic ulcerative stomatitis: A case report. *Journal of Periodontology*, *71*, 104–111. https://doi.org/10.1902/jop.2000.71.1.104

Molenda, I., & Kozlowski, Z. (2014). Przewlekle wrzodziejące zapalenie blony śluzowej jamy ustnei. Opis Przypadku. *Dental Forum*, *42*, 107–112.

Müller, S. (2017). Oral lichenoid lesions: Distinguishing the benign from the deadly. *Modern Pathology*, *30*, S54–S67. https://doi.org/10.1038/modpathol.2016.121

Mustafa, M. B., Porter, S. R., Smoller, B. R., & Sitaru, C. (2015). Oral mucosal manifestations of autoimmune skin diseases. *Autoimmunity Reviews*, *14*, 930–951. https://doi.org/10.1016/j.autrev.2015.06.005

Olszewska, M., Bańka-Wrona, A., Skrok, A., Rakowska, A., Górska, R., Solomon, L. W., & Rudnicka, L. (2016). Vulvovaginal-gingival Lichen Planus: Association with Lichen Planopilaris and stratified epithelium-specific antinuclear antibodies. *Acta Dermato Venereologica*, *96*, 92–96. https://doi.org/10.2340/00015555-2141

Olszewska, M., Jarząbek-Chorzelska, M., Kołacińska-Strasz, Z., Blaszczyk, M., & Jablońska, S. (1999). Przewlekłe wrzodziejące zapalenie jamy ustnej (*chronic ulcerative stomatitis* – CUS). Obserwacje kliniczne i immunologicz– ne u 20 pacjentów. *Przegląd Dermatologiczny*, *86*, 475–480.

Parodi, A., & Cardo, P. P. (1990). Patients with erosive lichen planus may have antibodies directed to a nuclear antigen of epithelial cells: A study on the antigen nature. *The Journal of Investigative Dermatology*, *94*, 689–693. https://doi.org/10.1111/1523-1747.ep12876269

Parodi, A., Cozzani, E., Cacciapuoti, M., & Rebora, A. (2000). Chronic ulcerative stomatitis: Antibodies reacting with the 70-kDa molecule react with epithelial nuclei. *British Journal of Dermatology*, *143*, 671–672. https://doi.org/10.1111/j.1365-2133.2000.03747.x

Parodi, A., Cozzani, E., Chorzelski, T. P., Beutner, E. H., & Rebora, A. (1998). A molecule of about 70 kd is the immunological marker of chronic ulcerative stomatitis. *Journal of the American Academy of Dermatology*, *38*, 1005–1006.

Parodi, A., Cozzani, E., Massone, C., Rebora, A., Priano, L., Ghigliotti, G., … Virno, G. (2007). Prevalence of stratified epithelium-specific antinuclear antibodies in 138 patients with lichen planus. *Journal of the American Academy of Dermatology*, *56*, 974–978. https://doi.org/10.1016/j.jaad.2005.10.033

Qari, H., Villasante, C., Richert, J., Rees, T., & Kessler, H. (2015). The diagnostic challenges of separating chronic ulcerative stomatitis from oral lichen planus. *Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology*, *120*, 622–627. https://doi.org/10.1016/j.oooo.2015.07.018

Reddy, R., Fitzpatrick, S. G., Bhattacharyya, I., Cohen, D. M., & Islam, M. N. (2018). Seventeen new cases of chronic ulcerative stomatitis with literature review. *Head and Neck Pathology*. https://doi.org/10.1007/s12105-018-0982-7

Rinaggio, J., Crossland, D. M., & Zeid, M. Y. (2007). A determination of the range of oral conditions submitted for microscopic and direct immunofluorescence analysis. *Journal of Periodontology*, *78*, 1904–1910. https://doi.org/10.1902/jop.2007.070095

Schmale, H., & Bamberger, C. (1997). A novel protein with strong homology to the tumor suppressor p53. *Oncogene*, *90*, 809–819. https://doi.org/10.1038/sj.onc.1201500

Solomon, L. W. (2008). Chronic ulcerative stomatitis. *Oral Diseases*, *14*, 383–389. https://doi.org/10.1111/j.1601-0825.2008.01446.x

Solomon, L. W., Aguirre, A., Neiders, M., Costales-Spindler, A., Jividen, G. J. Jr, Zwick, M. G., & Kumar, V. (2003). Chronic ulcerative stomatitis: Clinical, histopathologic, and immunopathologic findings. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology and Endodontics*, *96*, 718–726. https://doi.org/10.1016/S1079-2104(03)00459-1

Solomon, L. W., Neiders, M. E., Zwick, M. G., Kirkwood, K. L., & Kumar, V. (2007). Autoimmunity to deltaNp63alpha in chronic ulcerative stomatitis. *Journal of Dental Research*, *86*, 826–831. https://doi.org/10.1177/154405910708600904

Solomon, L. W., Stark, P. C., Winter, L., Kumar, V., & Sinha, S. (2010). ELISA test for p63 antibodies in chronic ulcerative stomatitis. *Oral Diseases*, *16*, 151–155. https://doi.org/10.1111/j.1601-0825.2009.01606.x

Wörle, B., Wollenberg, A., Schaller, M., Kunzelmann, K. H., Plewig, G., & Meurer, M. (1997). Chronic ulcerative stomatitis. *British Journal of Dermatology*, *137*, 262–265. https://doi.org/10.1046/j.1365-2133.1997.18171898.x

Yang, A., Kagdah, M., Wang, Y., Gillett, E., Fleming, M. D., Dötsch, V., … McKeon, F. (1998). P63 a p53 homolog at 3q27-29, encodes multiple products with transactivating, death inducing and dominant-negative activities. *Molecular Cell*, *2*, 305–316. https://doi.org/10.1016/S1097-2765(00)80275-0

How to cite this article: Azzi L, Cerati M, Lombardo M, et al. Chronic ulcerative stomatitis: A comprehensive review and proposal for diagnostic criteria. *Oral Dis*. 2019;25:1465–1491. https://doi.org/10.1111/odi.13001