

Received: 2010.09.21
Accepted: 2010.11.19
Published: 2010.12.17

Chronic ulcerative stomatitis (CUS). Lichen planus disseminatus, unguium pedis utriusque and pseudopelade

Monika Kapińska-Mrowiecka¹, Marzena Czubak-Macugowska¹, Adam Michcik², Piotr Chomik², Adam Włodarkiewicz²

¹ Department of Dermatology, S. Zeromski Specialist Hospital, Cracow, Poland

² Department of Oral and Maxillofacial Surgery, Medical University in Gdansk, Gdansk, Poland

Summary

Background:

Chronic erosive lesions in the oral cavity are usually difficult to diagnose and treat. Most frequently, the diagnosis is Candida infection, aphthosis, pemphigus or pemphigoid diseases. Chronic ulcerative stomatitis is a common condition of unknown etiology that affects the skin and mucous membranes and has been reported to occur mainly in females over 40 years old. Immunopathological and clinical examinations determine the diagnosis.

Case Report:

This study describes the case of a 70-year-old woman with chronic erosive lesions in the oral cavity on the buccal mucosa, tongue and lips. The patient had problems eating, but her general condition was good. Antifungal, antibiotic and local steroid therapy was not effective. We subsequently found disseminated skin and nail lesions characteristic of lichen planus. This suspicion was confirmed by histopathological examination. Other dermatological diseases, including oral lichen planus, pemphigus vulgaris and cicatricial pemphigoid, as well as bullous lupus erythematosus, were excluded. Indirect immunofluorescence (IIF) of the patient's serum using 2 appropriate substrates (monkey oesophagus at a titre of 1:640 and guinea pig oesophagus at a titre of 1:1280) revealed the presence of squamous epithelium-specific antinuclear antibodies (SES-ANA) of IgG. These are specific immunological markers of CUS.

Conclusions:

Hydroxychloroquine, given at a dosage of 400 mg/day, and a low dose of corticosteroids, led to complete remission of the mucosal, skin and nail lesions. A 4-year follow-up of the course of the disease, relapses, remissions and treatment are presented here.

key words:

chronic ulcerative stomatitis • lichen planus • hydroxychloroquine • corticosteroids

Full-text PDF:

<http://www.amjcaserep.com/fulltxt.php?ICID=881330>

Word count:

2455

Tables:

–

Figures:

9

References:

16

Author's address:

Piotr Chomik, Department of Oral and Maxillofacial Surgery, Medical University in Gdansk, Gdansk, Poland, e-mail: piotr.chomik@gumed.edu.pl

BACKGROUND

Chronic ulcerative stomatitis (CUS) is an uncommonly diagnosed disease. Since it was described for the first time by Jaremko et al. [1] in 1990, there have only been 39 cases of CUS reported [2]. Whether CUS is indeed an unusual disease, or whether its occurrence is much more common, remains controversial, but the clinical symptoms of CUS mimic other oral mucosal diseases, such as erosive lichen planus [3,4]. Both entities have a very similar clinical appearance.

On oral examination, erosive and ulcerative lesions of the mucosa are present, especially on the tongue, buccal mucosa and gums. In the latter the symptoms are the same as in desquamative gingivitis, which may lead to misdiagnosis and disguise the true occurrence of CUS [2,3]. Single cases of the disease localized on the labial and hard palate mucosa have also been described [4]. The entity most often affects females over 50 years old, although cases of CUS in younger women [3,5], as well as in males [6], have also been described. Patients mainly complain of chronic pain and a burning sensation in the oral cavity (burning mouth syndrome), tenderness and pain in the gums and tongue, and difficulties eating, resulting in weight loss. Alternating periods of exacerbation and remission of the symptoms are typical in the natural history of CUS. In particular cases, lesions in the oral cavity are accompanied by ophthalmic symptoms (cicatrical conjunctivitis), gluten-dependent enteropathies, and different skin lesions, including lichen planus and lichenoid lesions [6].

Microscopic examination of tissue specimens in the diagnostic course of CUS remains obligatory. The results of histological evaluation are usually not characteristic, and in most cases are typical for oral lichen planus. Stratified squamous epithelium expressing features of atrophy and parakeratosis, band-like infiltration of inflammatory cells, "saw-tooth" rete ridges, and the vacuolar degeneration of cells in the parabasal layers with replacement by eosinophilic clots and cell rests are present in haematoxylin and eosin-stained specimens [2–4].

Non-characteristic results of microscopic examination make the use of immunohistochemical diagnostic methods essential. Currently, direct immunofluorescence (DIF) serves as the gold standard in the diagnostic course of CUS. Indirect immunofluorescence (IIF) enables the exclusion of false negative and false positive results. Squamous epithelium-specific antinuclear antibodies (SES-ANA) – IgG class proteins – which are present in the nuclei of keratinocytes in the basal and parabasal layers of the epithelium, determine the diagnosis of CUS in immunofluorescent methods [3]. DIF involves *in situ* examination, whereas IIF detects SES-ANA in circulating blood, utilizing the appropriate tissue substrates: monkey and guinea-pig oesophagus.

Significant resistance to local corticosteroid, antibacterial and antifungal therapy, as well as professional oral hygiene procedures, is typical for CUS treatment. Moreover, erosions tend to intensify after discontinuation of such therapeutic schemes [2]. On the other hand, hydroxychloroquine at doses of 200–800 mg per day with supporting local corticosteroid therapy results in a significant reduction in symptoms, as well as improvement of the patient's general

well-being [2–4,7]. Chorzelski et al. [6] reported 3 cases in which remission of the disease appeared without any treatment, and 1 case in which significant improvement was achieved after consuming a gluten-free diet. Constant monitoring of oral hygiene, especially periodontal status, is particularly important because dental and dentogingival plaque, which are reservoirs of microorganisms, may exacerbate the course of CUS and intensify pain.

Diagnostic difficulties that may occur in CUS patients are highlighted in the presented case. These stem from 2 fundamental facts. Firstly, the clinical symptoms of CUS are very similar to numerous, more common, skin and oral mucosa diseases presenting as erosions and ulcerations, such as pemphigus vulgaris, bullous pemphigoid, mucous membrane pemphigoid, linear IgA disease, dermatitis herpetiformis, stomatitis herpetiformis, epidermolysis bullosa acquisita and systemic lupus erythematosus (SLE) [4]. Secondly, some of the diseases mentioned above may coincide with CUS, sharing the same clinical symptoms, as observed in the presented case.

CASE REPORT

A female patient (T.M.), aged 68, was treated from July 2005 for painful erosions and ulcerations, localized mainly on the buccal mucosa and lips (Figure 1). Initial dermatological and dental treatment included generally (Diflucan, Ketokonazol) and locally (Hascofungin, Bactroban) administered antifungal drugs, as well as locally administered glucocorticosteroids. This pharmacotherapeutic approach did not lead to any improvement. Simultaneously, an oral swab revealed an increased level of *Candida albicans*. In September 2005 the patient reported to the Department of Dermatology, S. Żeromski Specialist Hospital in Cracow, Poland, due to deterioration of the oral mucosa, intensification of pain and difficulties in eating. During admission, the patient reported that a few months earlier single violet-colored papules had appeared on the skin of the rear side of her thighs, palms, wrists and back, which became covered with scabs (Figures 2–4). About 2 months earlier, foci of alopecia with features of cicatrization had appeared on the skin of the parietal area (Figure 5). Additionally, the patient reported the feeling of a foreign body in the left eye (Fig. 6). Other complaints included a dry cough. Eight years earlier she was hospitalized because of bronchitis and was prescribed inhaled drugs for the following 4 years. The patient experienced 2 natural childbirths. In 1993 she underwent hysterectomy due to myomas. At the time of admission, she was treated with enalapril because of hypertension. Moreover, she complained of chronic stool impactions, and colonoscopy revealed the presence of colonic diverticula. Familial anamnesis was not characteristic.

Laboratory tests included physiological standards. X-ray examination of the thorax revealed peribronchial lesions in the right cardiophrenic angle, with a properly positioned diaphragm, enlarged heart and elongated thoracic aorta. X-ray examination of the thorax pulmonary fields showed no infiltrative lesions. Peribronchial fibrosis was observed at the lower pole of the right pulmonary niche. The ribodiaphragmic angles were clear.

Ophthalmological examination revealed conjunctivitis (Figure 6). Clinical and laboratory investigation relevant



Figure 1. Disseminated and painful erosions and ulcerations of the buccal mucosa and lower lip.



Figure 2. Violet-colored papules covered with a scab on the skin of the palms and wrists.



Figure 3. Violet-colored papules covered with a scab on the skin of the rear side of the thighs.



Figure 4. Violet-colored papule on the skin of the back.

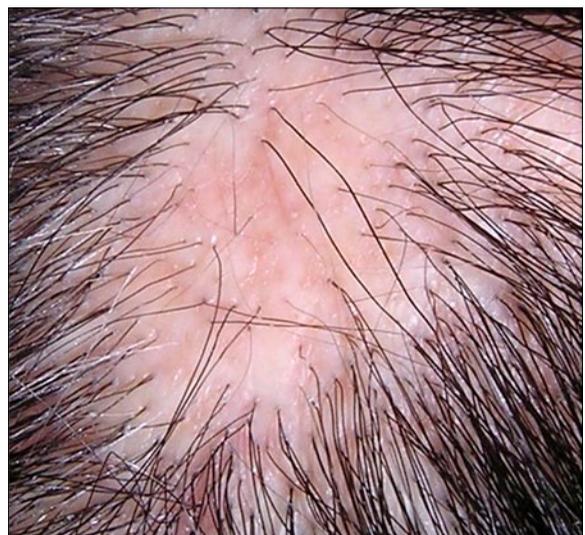


Figure 5. Focus of alopecia with features of cicatrization on the skin of the parietal area.



Figure 6. Clinical picture of conjunctivitis. The patient reported the feeling of a foreign body in the left eye.

to erosive oral lichen planus, aphthosis, pemphigus vulgaris, cicatricial pemphigoid and candidiasis was performed.

Mycological tests from toenail raspings were negative, both in the direct specimen and in culture.

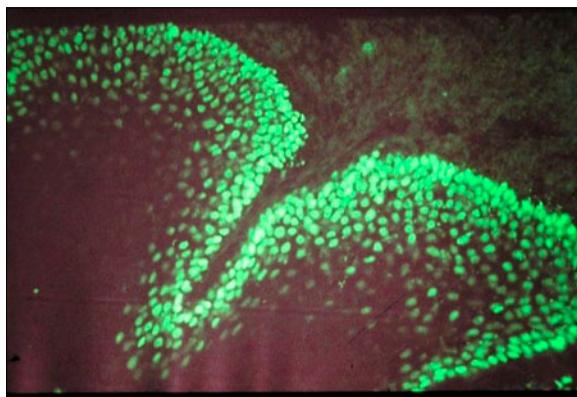


Figure 7. SES-ANA (Squamous epithelium-specific antinuclear antibodies). Indirect immunofluorescence (IIF) on monkey oesophagus – fluorescence of keratinocytes in basal and parabasal layer (courtesy of Dr. Zofia Kołacińska-Strasz).

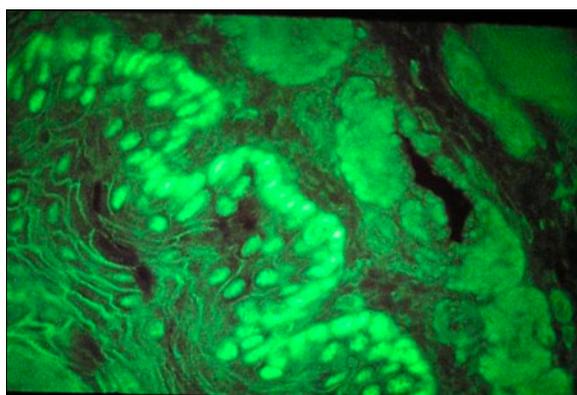


Figure 8. ES-ANA (Squamous epithelium-specific antinuclear antibodies). Indirect immunofluorescence (IIF) on guinea pig oesophagus – fluorescence of keratinocytes only in basal layer (courtesy of Dr. Zofia Kołacińska-Strasz).

Antibodies against both pemphigus and pemphigoid were absent in the blood serum.

Scalpel biopsies from the oral mucosa and skin lesion of the thigh were taken for histological evaluation. An inflammatory infiltrate consisting mainly of lymphocytes was revealed under the oral epithelium, but there were no alterations within the epithelium. Skin biopsy evaluation showed histological features typical for lichen planus.

Consequently, diagnostic tests for chronic ulcerative stomatitis (CUS) were performed. Direct immunofluorescence (DIF) of the oral mucosa specimen did not reveal either SES-ANA or other immunological features of CUS *in vivo*. Immunoserum against human IgG, IgA, IgM, and C3 complement were utilized in the test. Since the DIF result was negative, indirect immunofluorescence (IIF) was performed. SES-ANA at a titre of 1:640 on monkey oesophagus (Figure 7) and 1:1280 on guinea pig oesophagus (Figure 8) was revealed in the blood serum. The diagnosis of CUS was made assuming that the DIF result was false negative, probably because the tissue specimen was taken straight from the lesion without any of the surrounding unaltered mucosa, which prevented the appropriate immunopathological evaluation.



Figure 9. Clinical picture during treatment. Ulcerations and erosions in the oral cavity and lower lip were almost totally healed.

The following therapeutic scheme was utilized: hydroxychloroquine at a dose of 400 mg per day, methylprednisolone at a dose of 16 mg per day and local antiseptics. On the fifth day of treatment there was a considerable improvement in the patient's status. Ulcerations and erosions in the oral cavity and lips were almost totally healed (Figure 9). The therapy was continued, with a gradual reduction of methylprednisolone down to 4 mg per day. From 2007 until present, the patient has been treated with methylprednisolone at a maintenance dose of 4 mg per day and hydroxychloroquine at a dose of 200 mg per day, and 0.1% tacrolimus ointment is administered locally.

In the course of the disease, mucosal lesions tend to relapse after the withdrawal of methylprednisolone and hydroxychloroquine. The administration of the latter enables the maintenance of a relatively good local state, although oral mucosal lesions partially persist. The combination of methylprednisolone and hydroxychloroquine results in spectacular improvement of the local state and the total regression of clinical symptoms. On the other hand, methylprednisolone in monotherapy maintains a good clinical status, but oral mucosal lesions do not totally regress. Enhancement of the therapy by locally administered 0.1% tacrolimus resulted in a considerable improvement in the local state, but this proved to be insufficient in monotherapy. Within the 4-year follow-up, skin and nail lesions were successfully eliminated. However, regarding pseudopelade, the lesions were persistent and did not recede.

The patient remains under permanent dermatological control.

DISCUSSION

CUS is for many reasons very difficult to diagnose in everyday clinical practice, both for periodontologists and dermatologists. Diagnostic obstacles result from non-specific complaints that are common to a variety of entities, as well

as the frequent coincidence of CUS with such entities, thus camouflaging the symptoms. In addition, the diagnosis of CUS is hampered by the very similar clinical manifestations of other oral mucosa diseases, such as erosive lichen planus, mucous membrane pemphigoid, herpetic stomatitis, desquamative gingivitis and vegetant pyostomatitis [4,8].

The tendency of CUS to coincide with skin type lichen planus has been observed [9]. Solomon et al. [3] reported that biopsy-proven skin type lichen planus appeared in approximately 14% of CUS cases described. The case presented here lends support to this conclusion.

Therefore, DIF and IIF to reveal CUS-specific markers are essential to confirm the diagnosis of CUS. These markers are SES-ANA (squamous epithelium-specific antinuclear antibodies), which are IgG class molecules directed against the nuclei of keratinocytes in the basal and parabasal layers of the epithelium. This autoimmunological reaction is considered by some authors as the probable etiopathogenetic mechanism of the disease [8–11]. SES-ANA are present both in the nuclei of keratinocytes, where they are revealed by DIF, and in circulating blood. IIF utilizing heterogenic tissue specimens (monkey oesophagus and guinea-pig oesophagus) enables the identification of SES-ANA in circulating blood, and eventually verifies the false negative result of DIF. It is possible, however, that SES-ANA evaluation in DIF may be negative because the epithelial specimen tested is too slender, atrophic, is incised too tangentially to the surface, or is obtained only from the lesion without the surrounding mucosa [2]. In such cases, the IIF result is considered definitive. IIF is also helpful in the verification of false positive results of DIF, since SES-ANA are also present in various autoimmune disorders, such as lupus erythematosus, scleroderma or mixed connective tissue disease. In such entities, however, SES-ANA are present throughout the full thickness of the epithelium, not only in the basal and parabasal layers [8]. IIF determines the final result in cases of clinical doubt.

Observation of CUS patients revealed that the level of SES-ANA in blood serum and in tissues does not correlate with the intensification of clinical symptoms. Moreover, SES-ANA remain in blood serum during remission and after total regression of the lesions [7,8]. It is not known whether people who have SES-ANA in blood serum will suffer from CUS in the future [8].

SES-ANA are directed against nuclear antigen CUSP (chronic ulcerative stomatitis protein) [10,11]. CUSP is a protein with a molecular weight of approximately 70 kDa. The first reports concerning this autoantigen were published by Parodi et al at the end of the 20th century [12].

As a result of DNA sequencing, it was discovered that CUSP is a skin isoform of the p63 protein, known as $\Delta Np63\alpha$. It is also homologous to the antioncogenes p53, p73, as well as KET. These proteins are products of the p63/p51/p40/KET gene and arise due to alternative splicing [13].

In comparison to p53, CUSP does not have an N-terminal transactivation domain. *In vitro* studies showed that CUSP blocks the function of the p53 protein. Whether this property brings the possibility of enhanced neoplastic transformation is yet to be verified [11].

The sera of patients with immunologically proven CUS, but without clinical manifestations, contain 2 different autoantigens: 1 with a molecular weight of 70 kDa and another of 180 kDa [12].

Another 2 autoantigens may be found in the sera of patients with pemphigus and bullous pemphigoid: 1 with a molecular weight of 130 kDa and another of 230 kDa. These autoantigens are not the same as CUSP. The sera of patients with lupus erythematosus do not contain autoantigens analogous to CUSP.

The first attempts at CUS treatment were based on corticosteroids administered both locally and generally. This approach proved to be insufficient. The rapid relapse of symptoms after discontinuation of treatment, or even a dose reduction, was typical. Presently, the treatment of choice in CUS management is a combination therapy consisting of antimalarials administered generally and supporting local corticosteroid therapy. Hydroxychloroquine is a basic medication and its mechanism of action includes the modification of endocellular processes.

Hydroxychloroquine increases endocellular alkaline reactions, which in turn decrease the intensity of biochemical inflammatory processes. The degradation of proteins by acidic hydrolases in lysosomes is reduced, as is the assembly of macromolecules in endosomes and the post-translation modification of proteins in the Golgi apparatus [14]. Hydroxychloroquine decreases the infiltration of inflammatory cells, particularly T lymphocytes, in stromal tissues.

The basic and most beneficial mechanism of action of hydroxychloroquine in CUS is interference with the activation of macrophages and other antigen-presenting cells. As a result, preparation of the antigen for presentation on the cell surface is disturbed, and consequently, the reaction between the autoantigen and autoantibody is impaired. This mechanism is known as antigen processing. Additionally, *in vitro* studies have revealed that hydroxychloroquine reduces the release of IL-1, IL-6 and TNF α from monocytes and T lymphocytes [15].

Data from the literature also indicate that hydroxychloroquine affects lipid metabolism.

Studies by Woźniacka et al proved that 3 months of therapy at 250 mg per day considerably reduced the levels of total cholesterol, LDL, and triglycerides, which resulted in a decreased risk of atherosclerosis.

An additional advantage deriving from hydroxychloroquine therapy is the reduction of the side effects of glucocorticosteroids [16].

In the reported case, after initial diagnosis of erosive lichen planus, local application of corticosteroids did not result in any improvement. Administration of hydroxychloroquine in combination with corticosteroids led to considerable remission of the symptoms.

CONCLUSIONS

To summarize, CUS is a rarely diagnosed autoimmunological disease, which tends to coincide with other systemic

diseases, primarily lichen planus. There are also other clinical entities with similar clinical symptoms, for example: pemphigus vulgaris, pemphigoid, desquamative gingivitis, and herpetic stomatitis.

It is suggested that the true frequency of CUS is higher than estimated, mainly due to misdiagnosis as erosive lichen planus, which has similar clinical symptoms.

Clinical confirmation of CUS follows resistance to corticosteroid therapy and significant remission of symptoms after administration of antimalarials.

Acknowledgements

The authors would like to thank Dr. Zofia Kołacińska-Strasz for performing and interpreting the immunopathological tests and Prof. Stefania Jabłońska for her comments on the immunopathological tests.

REFERENCES:

- Jaremko WM, Beutner EH, Kumar V et al: Chronic ulcerative stomatitis associated with a specific immunologic marker. *J Am Acad Dermatol*, 1990; 22(2 1): 215–20
- Islam MN, Cohen DM, Ojha J et al: Chronic ulcerative stomatitis: diagnostic and management challenges – four new cases and review of literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*, 2007; 104: 194–203
- Solomon LW, Aguirre A, Neiders M et al: Chronic ulcerative stomatitis: clinical, histopathologic and immunopathologic findings. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*, 2003; 96: 718–26
- Solomon LW: Chronic ulcerative stomatitis. *Oral Diseases*, 2008; 14: 383–89
- Woerle B, Wollenberg A, Schaller M et al: Chronic ulcerative stomatitis. *Br J Dermatol*, 1997; 137: 262–65
- Chorzelski TP, Olszewska M, Jarząbek-Chorzelska M, Jabłonska S: Is chronic ulcerative stomatitis an entity? Clinical and immunological findings in 18 cases. *Eur J Dermatol*, 1998; 8(4): 261–65
- Lewis JE, Beutner EH, Rostami R, Chorzelski TP: Chronic ulcerative stomatitis with stratified epithelium-specific antinuclear antibodies. *Int J Dermatol*, 1996; 35: 272–75
- Szymanek M, Krasowska D: Chronic ulcerative stomatitis – pathogenesis, clinical manifestations and therapy. *Post Dermatol Alergol*, 2009; XXVI, 6: 518–21
- Bańka-Wrona A, Kołacińska-Strasz Z, Łabęcka H et al: Chronic ulcerative stomatitis. Relation to lichen planus. *Przegl Dermatol*, 2009; 96: 400–5
- Lee LA, Walsh P, Prater CA et al: Characterization of an autoantigen associated with chronic ulcerative stomatitis: the CUSP autoantigen is a member of the p53 family. *J Invest Dermatol*, 1999; 113: 146–51
- Dellavalle RP, Walsh P, Marchbank A et al: CUSP/p63 expression in basal cell carcinoma. *Exp Dermatol*, 2002; 11: 203–8
- Parodi A, Cozzani E, Chorzelski TP et al: A molecule of about 70 kD is the immunologic marker of chronic ulcerative stomatitis. *J Am Acad Dermatol*, 1998; 38: 1005–6
- Senoo M, Tsuchiya I, Matsumura Y et al: Transcriptional dysregulation of the p73L/p63/p51/p40/KET gene in human squamous cell carcinomas: expression of ΔNp73L, a novel dominant-negative isoform, and loss of expression of the potential tumour suppressor p51. *Br J Cancer*, 2001; 84(9): 1235–41
- Fox RI: Mechanism of action of hydroxychloroquine as an antirheumatic drug. *Semin Arthritis Rheum*, 1993; 23(2 Suppl.1): 82–91
- Sperber K, Quraishi K, Kalb TH et al: Selective regulation of cytokine secretion by hydroxychloroquine: inhibition of interleukin-1 alpha and interleukin-6 in human monocytes and T cells. *J Rheumatol*, 1993; 20: 803–8
- Woźniacka A, Lesiak A, Smigielski J, Sysa-Jedrzejowska A: Chloroquine influence on lipid metabolism and selected laboratory parameters. *Przegl Lek*, 2005; 62(9): 855–59