



Title	Mucosal lesions in cutaneous lupus erythematosus successfully treated with hydroxychloroquine
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1 Mucosal lesions in cutaneous lupus erythematosus successfully treated with
2 hydroxychloroquine

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6 Running head: HCQ for mucosal lesions

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5

6

7 **Abbreviation**

8 HCQ: Hydroxychloroquine, SLE: systemic lupus erythematosus, CLE: cutaneous lupus

9 erythematosus,

10

11

12 **Abstract**

13 Cutaneous lupus erythematosus (CLE) is a rare, potentially disfiguring, chronic

14 autoimmune disease with extremely variable skin and mucosal membrane

15 manifestations. Hydroxychloroquine (HCQ) is an antimalarial drug that has been used

16 in various countries to treat autoimmune diseases including CLE. HCQ was banned for

17 a long time in Japan because of severe chloroquine retinopathy and was reapproved as a

1 first-line treatment for CLE in 2015. There are no case reports describing the
2 effectiveness of HCQ for CLE with oral mucosal lesions in the dental field. We present
3 a case of CLE whose oral lesions were successfully treated with HCQ.

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5 Key words: mucosal lesion, hydroxychloroquine, cutaneous lupus erythematosus

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11 **Introduction**

12 Hydroxychloroquine (HCQ) is an antimalarial drug that has been used commonly in
13 various countries to treat systemic lupus erythematosus (SLE), cutaneous lupus
14 erythematosus (CLE), rheumatoid arthritis and other inflammatory diseases¹. HCQ was
15 banned for a long time in Japan because of severe chloroquine retinopathy and was
16 reapproved in 2015 as a first-line treatment for CLE². CLE manifestations are

1 wide-ranging, occasionally including mucous involvement of the lip, the tongue, and
2 the buccal and nasal mucosa³. It is essential for dental practitioners to be familiar with
3 CLE clinical manifestations and treatments, because CLE patients may present at dental
4 clinics for their initial and main manifestations. However, in the field of dental medicine,
5 no cases have addressed the effectiveness of HCQ for oral mucosal lesions in CLE. We
6 present a case of CLE whose oral lesions were successfully treated with HCQ in close
7 cooperation with dermatologists.

8

9 **Case Report**

10 A 76-year-old male was referred to the dental medicine and dermatology departments of
11 our institution with a 12-month history of erosions on the lower lip and a 16-month
12 history of erythematous macules on the skin. Physical examinations revealed multiple
13 infiltrating erythematous plaques on the back, arms and palms, and painful erosions on
14 the lower lip (Fig. 1-A, B). Histopathological examinations of mucosa from the lower
15 lip revealed hyperkeratosis, the thinning of the epithelium and the vacuolar
16 degeneration of the basal cell layer accompanied by noticeable civatte bodies on the

1 epidermis (Fig. 2-A). Perivascular infiltrates of lymphocytes and plasma cells
2 associated with interstitial mucin deposition were observed in the dermis (Fig. 2-B).
3 Direct immunofluorescence showed linear deposition of C3 and IgM at the basement
4 membrane zone (Fig3-A). Multiple Civatte bodies within the epidermis were clearly
5 detected by fibrinogen staining (Fig3-B). Systemic involvement suggestive of SLE,
6 such as renal dysfunction, hemolytic anemia and neurologic disease, was not detected.
7 Considering all of the findings, we diagnosed the case as CLE with oral mucosal lesions.
8 We administered a topical steroid and an oral rinse of azulene sodium sulfanate, which
9 proved ineffective. Therefore, HCQ (200 mg and 400 mg on alternate days) was
10 introduced. By 1 month later, the multiple rashes on the skin and erosions on the oral
11 mucosa had resolved (Fig. 4-A,B, Fig. 5).

12

13 **Discussion**

14 Several previous studies described the favorable response of CLE to HCQ therapy. One
15 study revealed that 15 out of 30 CLE patients treated with HCQ showed improvement⁴.
16 A recent study showed a 61% response to HCQ in CLE⁵. In Japan, a clinical study

1 showed HCQ to be effective against CLE, with more than 80% of patients responding
2 favorably⁶. Many studies have reported on the efficacy of HCQ for cutaneous lesions in
3 CLE; however, no previous studies have reported the results of HCQ treatment for oral
4 lesions in CLE. We present the first case of CLE whose treatment with HCQ was
5 successful not only for the skin lesions but also for the oral mucosal lesions.

6

7 The clinical, serological and histological findings are crucial for diagnosing CLE.
8 Previous studies have shown that 40% of SLE cases and 10-20% of CLE cases have
9 mucous involvement⁷. In the present case, however, lichen planus and Sjögren syndrome
10 were considered as differential diagnoses. Lichen planus histologically shows the
11 infiltration of T cells in a band-like pattern in the dermis⁸, but the present case showed
12 perivascular infiltrates of lymphocytes and plasma cells associated with mucin
13 deposition, suggesting CLE. A diagnosis of Sjögren syndrome is usually made on the
14 basis of formal criteria, which requires the dryness of the mouth and eyes, and the
15 immunological abnormalities such as the presence of serum anti-SSA antibodies or
16 focal lymphocytic sialadenitis in a biopsy of the labial salivary glands⁹. The present

1 case had no symptoms of eye dryness, and no lymphocytic infiltration around the minor
2 salivary glands. Therefore, this case did not meet the diagnostic criteria of Sjögren
3 syndrome¹⁰. Furthermore, the cutaneous manifestation in this case were not consistent
4 with the typical findings of Sjögren syndrome¹¹. Taking all the findings into
5 consideration, we diagnosed the case as CLE with oral mucosal lesions. Our patient
6 reported painful stomatitis and insufficient dietary intake. Topical steroid treatment
7 showed no effect. However, by 4 weeks after the start of HCQ administration, the
8 erosions on the oral mucosa and rashes on the skin had disappeared. Notably, the
9 remarkably rapid remission of intraoral pain from the lip erosions greatly improved the
10 patient's QOL. According to a previous study, HCQ did not improve symptoms in
11 Sjögren syndrome when tested against a placebo¹². In contrast, the present case showed
12 significant improvement after the administration of HCQ, which is consistent with our
13 definitive diagnosis.

14

15

16 This case clearly shows that HCQ improves not only the cutaneous manifestations but

1 also the oral mucous manifestations of CLE. When refractory oral mucous erosions
2 related to CLE are observed, we should consider the possibility of CLE with oral
3 mucosal lesions in consultation with dermatologists. HCQ might improve those
4 manifestations. For prompt diagnosis, we need to recognize the possibility of CLE, and
5 for successful treatment we need to establish relationships with dermatologists.

6

7 The authors declare that there are no conflicts of interest associated with this
8 manuscript.

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1 References

- 2 1 Rainsford KD, Parke AL, Clifford-Rashotte M, Kean WF. Therapy and
3 pharmacological properties of hydroxychloroquine and chloroquine in treatment of
4 systemic lupus erythematosus, rheumatoid arthritis and related diseases.
5 *Inflammopharmacology* 2015; 23:231–69.
- 6 2 Yokogawa N, Eto H, Tanikawa A, *et al.* Effects of Hydroxychloroquine in Patients
7 With Cutaneous Lupus Erythematosus: A Multicenter, Double-Blind, Randomized,
8 Parallel-Group Trial. *Arthritis Rheumatol* 2017; 69:791–9.
- 9 3 Lauren G Okon VPW. Cutaneous Lupus Erythematosus: Diagnosis and treatment.
10 *Best practice & research Clinical rheumatology* 2013; 27:391–404.
- 11 4 Bezerra ELM, Vilar MJP, da Trindade Neto PB, Sato EI. Double-blind,
12 randomized, controlled clinical trial of clofazimine compared with chloroquine in
13 patients with systemic lupus erythematosus. *Arthritis Rheum* 2005; 52:3073–8.
- 14 5 Chasset F, Bouaziz JD, Costedoat-Chalumeau N, *et al.* Efficacy and comparison of
15 antimalarials in cutaneous lupus erythematosus subtypes: a systematic review and
16 meta-analysis. *Br J Dermatol* 2017; 177:188–96.
- 17 6 Yokogawa N, Tanikawa A, Amagai M, *et al.* Response to hydroxychloroquine in
18 Japanese patients with lupus-related skin disease using the cutaneous lupus
19 erythematosus disease area and severity index (CLASI). *Mod Rheumatol* 2013;
20 23:318–22.
- 21 7 López-Labady J, Villarroel-Dorrego M, González N, *et al.* Oral manifestations of
22 systemic and cutaneous lupus erythematosus in a Venezuelan population. *Journal*
23 *of Oral Pathology & Medicine* 2007; 36:524–7.
- 24 8 Alrashdan MS, Cirillo N, McCullough M. Oral lichen planus: a literature review
25 and update. *Arch Dermatol Res* 2016; 308:539–51.
- 26 9 Mariette X, Criswell LA. Primary Sjögren's Syndrome. *N Engl J Med* 2018;
27 378:931–9.

- 1 10 Shiboski CH, Shiboski SC, Seror R, *et al.* 2016 American College of
2 Rheumatology/European League Against Rheumatism classification criteria for
3 primary Sjögren's syndrome. *Annals of the Rheumatic Diseases* 2017; 76:9–16.
- 4 11 Generali E, Costanzo A, Mainetti C, Selmi C. Cutaneous and Mucosal
5 Manifestations of Sjögren's Syndrome. *Clin Rev Allergy Immunol* 2017; 53:357–
6 70.
- 7 12 Gottenberg J-E, Ravaud P, Puéchal X, *et al.* Effects of hydroxychloroquine on
8 symptomatic improvement in primary Sjögren syndrome: the JOQUER
9 randomized clinical trial. *JAMA* 2014; 312:249–58.
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1

2 Figure legends

3 Figure 1 The initial clinical manifestations.

4 A) Erosions on the lower lip (black arrow). B) Multiple erythematous plaques on the
5 back.

6

7 Figure 2 Histological findings.

8 A) A mucous biopsy specimen taken from the lower lip shows inflammatory infiltrates
9 in the lamina propria (scale bar=100 μ m). B) Perivascular infiltrates of lymphocytes are
10 observed (scale bar=50 μ m).

11

12 Figure 3 Immunological findings.

13 A) Direct immunofluorescence from the same specimen shows linear deposition of IgM
14 at the basement membrane zone (white arrowhead) (scale bar=100 μ m). B) Multiple
15 Civatte bodies in the epidermis are detected by fibrinogen staining (white arrowhead)
16 (scale bar=100 μ m).

1

2 Figure 4 The clinical manifestations after HCQ administration.

3 C) The painful erosions have disappeared. D) The erythematous plaques on the upper
4 back have improved.

5

6 Figure 5 The clinical courses of the back skin and oral mucous lesions, and

7 administration of the medications. TACR: tacrolimus topical treatment, AZ: azulen

8 sodium sulfonate oral rinse, HCQ: hydroxychloroquine oral administration (200 mg and

9 400 mg on alternate days). ▲: First visit.

10

Figure 1

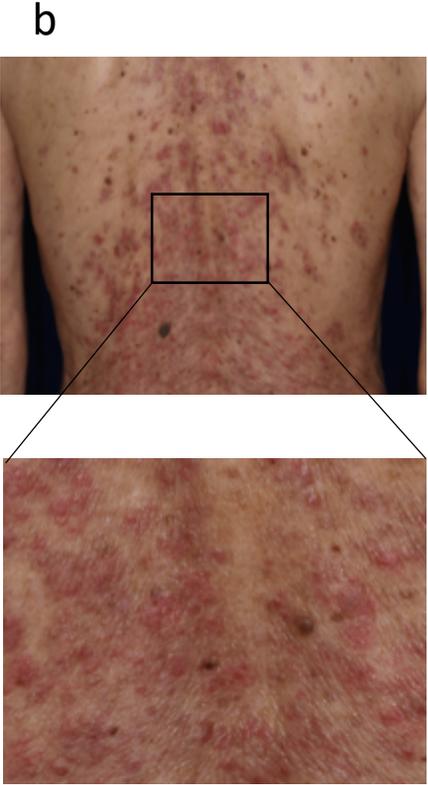
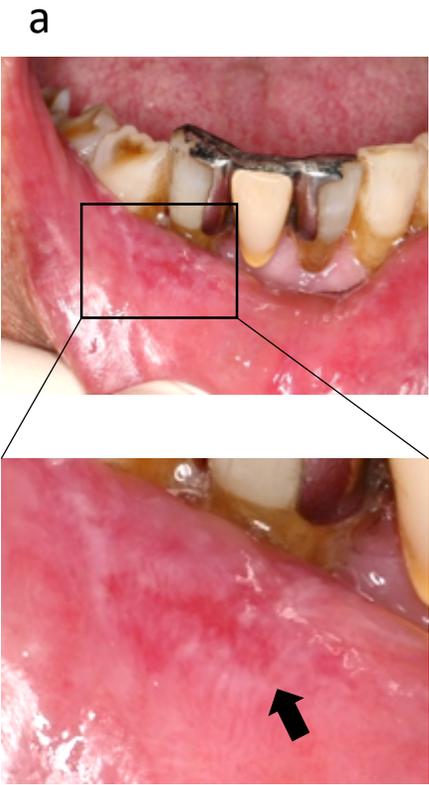
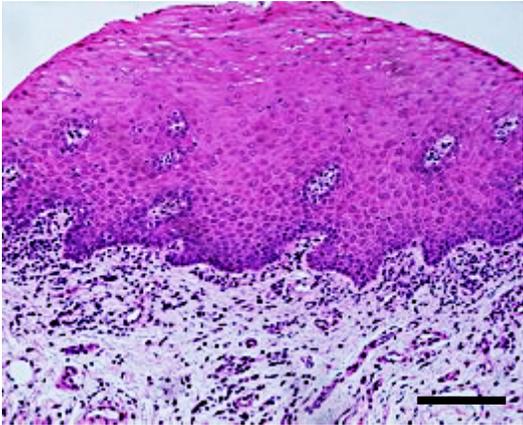


Figure 2

a



b

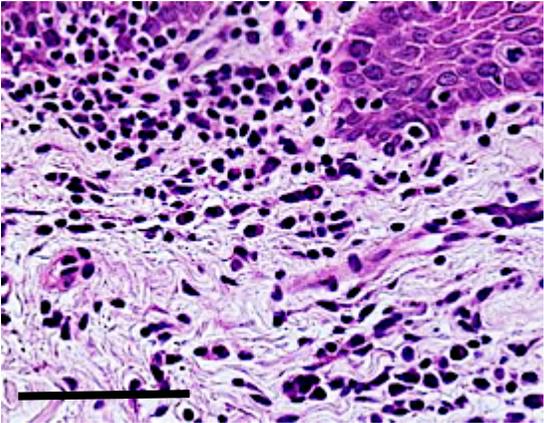
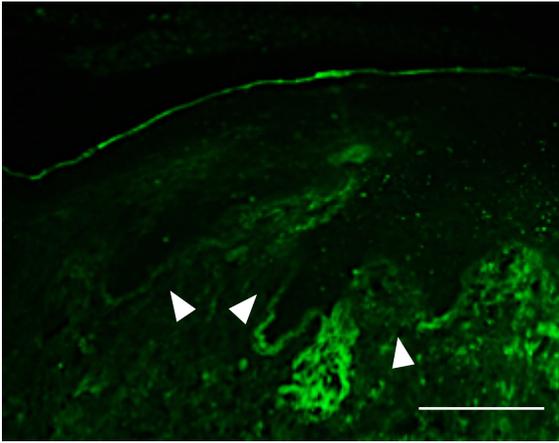


Figure 3

a



b

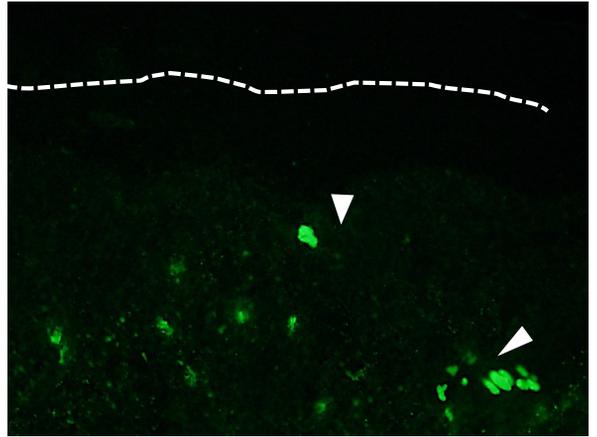
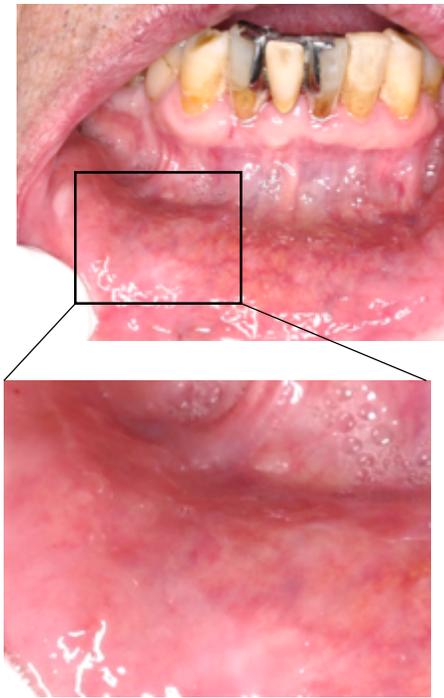


Figure 4

a



b

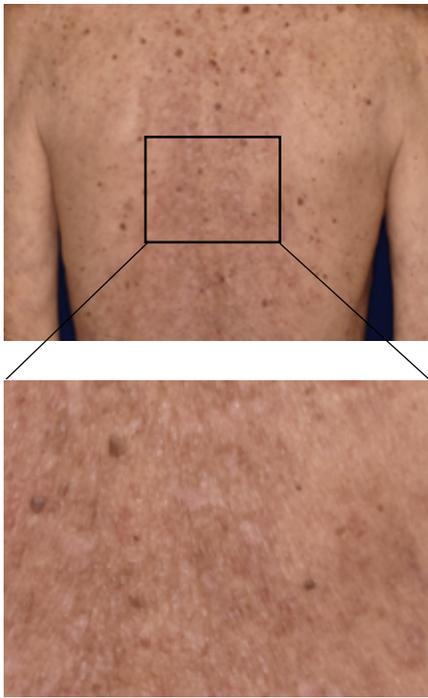


Figure 5

