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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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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

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

Key words: mucosal lesion, hydroxychloroquine, cutaneous lupus erythematosus

Introduction

Hydroxychloroquine (HCQ) is an antimalarial drug that has been used commonly in various countries to treat systemic lupus erythematosus (SLE), cutaneous lupus erythematosus (CLE), rheumatoid arthritis and other inflammatory diseases¹. HCQ was banned for a long time in Japan because of severe chloroquine retinopathy and was 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.

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

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

Discussion

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

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

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

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

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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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.

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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

Figure 4

a

b

Figure 5