



Figure 1. Clinical and histopathological features results. (A) Skin lesion on the nose and (B) on the left cheek. (C, D) Histopathological features (H&E). (E) Skin lesions after treatment on the left cheek.

Histopathology of a skin biopsy revealed epidermal changes included hyperkeratosis with follicular plugging, basal cell vacuolization, and interface dermatitis (Figure 1C) and atypical epidermal keratinocytes (Figure 1D). DIF studies were negative.

We diagnosed discoid lupus erythematosus (DLE) with unresponsive to topical clobetasol propionate 0.05% and tacrolimus 0.1% for several years. Oral HCQ (300 mg daily) started. However, 2 weeks later as diarrhea appeared frequently as an side effect, decreased HCQ (200 mg daily) provided and the side effect moderately improved. The patient who had a history of chronic urticaria also complained about urticarial reaction more frequently 3 weeks later, which was improved with epinastine (10 mg daily) combination. The primary end point was judged by the change in the cutaneous lupus erythematosus disease area and severity index (CLASI) activity score following of HCQ treatment^[2-4]. The CLASI activity score improved from 11 to 5 for 3 months. After 4 months, the patient was improved with a remarkable decrease in the size of the bilateral cheeks (Figure 1E) and the changes of the pigmentation of the nose.

Discussion

The diverse immune modulatory effects of HCQ make it widely used in treatment of autoimmune diseases. In this case, HCQ enhanced urticarial reaction frequently, which represents an unusual, although probably under recognized complication.

The withdrawal of HCQ treatments due to adverse cutaneous eruptions was previously reported in approximately 3% of patients^[5]. The Japanese report on side effect of HCQ from September 7, 2015 to April 30, 2017 was 165 cases of 122 patients (unpublished data from the company). The majority of the data comprise skin disorder and gastrointestinal disorders such as diarrhea, and there are 2 cases of urticaria. It is sometimes difficult to establish whether early cutaneous eruptions that appear after the initiation of oral HCQ are due to HCQ or a flare of disease^[6].

The patient remarkably responded to anti-histamines, we have hypothesized that the level of urticarial reaction threshold might decrease as HCQ suppresses the activity of the innate immune system. It is hard to answer to this hypothesis. However, our recent experiments of mast cells suggested that mast cells are biphasic-reaction in the skin lesions^[7,8]. The HCQ effects on mast cell biology will be expected for better treatment of CLE^[9].

References

1. Wallace DJ, Gudsoorkar VS, Weisman MH, *et al.* New insights into mechanisms of therapeutic effects of anti-malarial agents in SLE. *Nat Rev Rheumatol* 2012; 8(9): 522–533. doi: 10.1038/nrrheum.2012.106.
2. Yokogawa N, Eto H, Tanikawa A, *et al.* Effects of hydroxychloroquine in patients with cutaneous lupus erythematosus : A multi-center, double-blind, randomized, parallel-group trial. *Arthritis Rheumatol* 2017; 69(4): 791–799. doi: 10.1002/art.40018.
3. Yokogawa N, Tanikawa A, Amagai M, *et al.* Response to hydroxychloroquine in Japanese patients with lupus-related skin disease using the cutaneous lupus erythematosus disease area and severity index (CLASI). *Mod Rheumatol* 2013; 23(2): 318–322. doi: 10.1007/s10165-012-0656-3.
4. Ikeda T, Kanazawa N, Furukawa F. Hydroxychloroquine administration for Japanese lupus erythematosus in Wakayama: A pilot study. *J Dermatol* 2012; 39(6): 531–535. doi: 10.1111/j.1346-8138.2011.01448.x.
5. Salido M, Joven B, D’Cruz DP, *et al.* Increased cutaneous reactions to hydroxychloroquine (Plaquenil) possibly associated with formulation change: Comment on the letter by Alarcon. *Arthritis Rheum* 2002; 46(12): 3392–3396. doi: 10.1002/art.10565.
6. Matsuda T, Nhung Thi My LY, Kambe N, *et al.* Early cutaneous eruptions after oral hydroxychloroquine in a LE patient: A case report and review of the literature. *J Dermatol* 2017. In Press.
7. Shimomatsu T, Kanazawa N, Mikita N, *et al.* The effect of hydroxychloroquine on lupus erythematosus-like skin lesions in MRL/lpr mice. *Mod Rheumatol* 2016; 26(5): 744–748. doi: 10.3109/14397595.2016.1140711.
8. Inaba Y, Kanazawa N, Yoshimasu T, *et al.* Severe lupus erythematosus-like skin lesions in MRL/lpr mice with homozygous *Kit^{wsh/wsh}* mutation. *Mod Rheumatol* 2017. In Press. doi: 10.1080/14397595.2017.1341591.
9. Furukawa F. Hydroxychloroquine in lupus erythematosus, a new horizon of the old drug. *Trends Immunol* 2017. In Press.