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LETTER TO THE EDITOR

Acute generalized exanthematous pustulosis due to hydroxychloroquine after a prolonged latent period

Dear Editor,

Acute generalized exanthematous pustulosis (AGEP) is a rare, but severe cutaneous adverse reaction induced by drugs such as antibiotics, calcium channel blockers, and NSAIDs. Hydroxychloroquine sulfate (HCQ), an antimalarial drug, is used worldwide, for the treatment of rheumatologic and dermatologic diseases, because of its anti-inflammatory and immunosuppressive properties. Herein, we report, to our knowledge, the first case of HCQ-induced AGEP in Japan.

A 55-year-old Japanese woman was first diagnosed with systemic lupus erythematosus (SLE) about 30 years ago. She had no personal or family history of psoriasis. She has been treated with 10 mg of oral prednisolone and 50 mg of azathioprine daily until recently. However, because of SLE exacerbations, 200 mg/d of HCQ was added to her regimen. Twenty-one days after starting HCQ treatment, she developed erythema and papules on the trunk with fever exceeding 39°C (Figure 1A). Her primary physician instructed her to discontinue HCQ, and her prednisolone dosage was increased to 50 mg daily. Three days later, her skin rash spreads and she developed numerous nonfollicular, erythematous pustules (Figure 1B). Histological examination revealed subcorneal neutrophilic pustules and edematous dermis (Figure 1C). Her white blood cell count was normal, but C-reactive protein level was elevated to 19.7 mg/dL (normal: <0.1). Intravenous methylprednisolone at 500 mg daily was administered for 2 days, followed by oral prednisolone at 60 mg daily. Subsequently, the skin lesions and fever resolved. She began to have recurring episodes of small papules in the intertriginous areas, a so-called smoldering eruption (Figure 1D). Prednisolone was tapered to her baseline dose over the following 6 weeks, and she made a complete recovery without relapse. The patch and drug lymphocyte stimulating tests were negative.

HCQ was previously believed to be a rare cause of AGEP. The EuroSCAR study revealed that patients treated with HCQ were at high risk

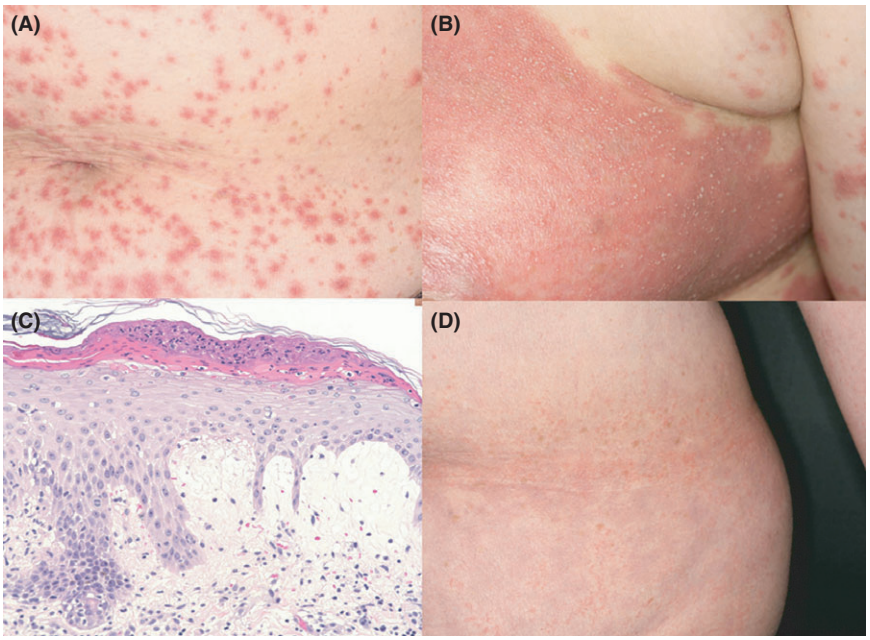

FIGURE 1 A, Multiple erythematous macules and nonfollicular papules on the abdomen at the onset of AGEP. B, Widespread erythema and numerous nonfollicular micropustules on the trunk three days after the onset of AGEP. C, Subcorneal neutrophilic pustules and severe dermal edema with mixed inflammatory cells. D, Smoldering small papules waxed and waned throughout the treatment period

for AGEP.[1] The U.S. Food and Drug Administration mandated a change in the HCQ drug information profile to include AGEP among the potential adverse reactions to the drug.[2] It was reported that the latent period of HCQ-induced AGEP is 12–30 days, which is much longer than that of antibiotic-induced AGEP, a latent period of only a few days.[1]

Although controversial, the mechanisms of HCQ-induced AGEP are thought to relate to its metabolic characteristics and immunologic dysregulation.[1]

Cases of prolonged latency in HCQ-induced AGEP have been previously reported.[3] It is thought that the long latency period for this condition is due to the long half-life of HCQ, which is approximately 40–60 days in blood.[4] Our patient required a longer time for complete resolution of the condition because of the waxing and waning "smoldering eruption" during the clinical course. It is possible that HCQ-induced AGEP is unique in its clinical course, unlike AGEP due to other drugs. As HCQ was approved domestically in 2015, Japanese dermatologists should be aware of the rare but severe adverse dermatologic reactions due to HCQ.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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