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Early-Onset Generalized Pustular Psoriasis of Pregnancy Following Hydroxychloroquine Use

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Generalized pustular psoriasis of pregnancy (GPPP), characterized by widespread sterile pustules and erythematous patches with systemic symptoms such as fever, is a rare form of pustular psoriasis. GPPP typically occurs in the third trimester of pregnancy and can be triggered by various factors such as infections, hypocalcemia, and drugs including *N*-butyl-scopolammonium bromide. We report a rare case of new-onset GPPP in a 33-year-old multigravida female at 17 weeks' gestation, which occurred earlier than usual, after taking hydroxychloroquine for 3 weeks to treat systemic lupus erythematosus. She stopped her medications and was treated with systemic corticosteroid, but without improvement. Her medication was changed to systemic cyclosporine; her skin lesions improved, which completely resolved after delivery. This is the first case of GPPP developed following hydroxychloroquine use for systemic lupus erythematosus, which occurred earlier than usual and completely resolved after delivery. This case demonstrates that hydroxychloroquine can induce GPPP before the third trimester of pregnancy.

Keywords: Cyclosporine, Hydroxychloroquine, Lupus erythematosus systemic, Pregnancy, Psoriasis

INTRODUCTION

Generalized pustular psoriasis of pregnancy (GPPP) typically occurs in the third trimester of pregnancy. It is a rare form of pustular psoriasis, characterized by widespread sterile pustules studded on erythematous patches with systemic symptoms such as fever, arthralgia, and leukocytosis[1]. The skin lesions usually begin within intertriginous areas, such as the axillae and skin folds of breasts, and spread centrifugally to extremities[2]. Annular-shaped erythematous plaques become confluent and may become eventuated with central clearing and desquamation[2]. GPPP usually resolves after delivery but can be a life-threatening condition for both mother and fetus[1]. Despite poorly understood mechanisms, IL36RN mutations, hypothyroidism, hypocalcemia, infections, and drugs such as *N*-butyl-scopolammonium bromide have been reported to potentially trigger GPPP[1,3].

Hydroxychloroquine (HCQ), a synthetic antimalarial drug, has been used worldwide to treat autoimmune disorders, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis[3]. However, its adverse effects including diarrhea, cardiac arrhythmia, conduction abnormalities, acute generalized exanthematous pustulosis (AGEP), plaque type psoriasis, and generalized pustular psoriasis (GPP) have been reported[4,5]. However, the induction of new-onset GPPP after taking HCQ is distinctly unusual.

Herein, we report a rare case of GPPP at 17 weeks' gestation, earlier than the typical third trimester of pregnancy, after taking HCQ to treat SLE, that was successfully maintained with systemic cyclosporine during pregnancy and completely resolved after delivery.

We received the patient's consent form about publishing all photographic materials.

CASE REPORT

A 33-year-old female (gravida 2 para 1) at 18 weeks' gestation presented with erythematous patches and pustules on the trunk and both extremities. She was diagnosed with SLE at 12 weeks' gestation when she was admitted for thrombocytopenia. She denied any personal or family history of psoriasis. She had a history of normal spontaneous vaginal delivery; at that time, her only problem was thrombocytopenia. The patient had been taking HCQ and aspirin for her SLE for a month and oral iron tablets for 7 days. After 3 weeks of HCQ treatment, she developed pruritic erythematous patches and pustules on her face and trunk at 17 weeks' gestation. On her first visit, clinical examination revealed erythematous patches and pustules on the trunk and both extremities, some of which were desquamated (Fig. 1A). A skin biopsy taken from the abdominal pustules showed subepidermal bullous lesion containing neutrophils and upper dermal neutrophilic infiltrate (Fig. 2A). Laboratory tests showed increased leukocyte (17,060/μl) and neutrophil (14,300/μl) counts, while routine liver and kidney function tests, serum complement, and the titer of the anti-dsDNA antibody level were normal.

We initially considered HCQ-induced AGEP because of the patient's pharmacological history, the clinical manifestation of erythematous patches and pustules with leukocytosis at 17 weeks' gestation, and the skin biopsy not showing any characteristic features of psoriasis. Under the suspicion of AGEP, she stopped her medications and was treated with systemic

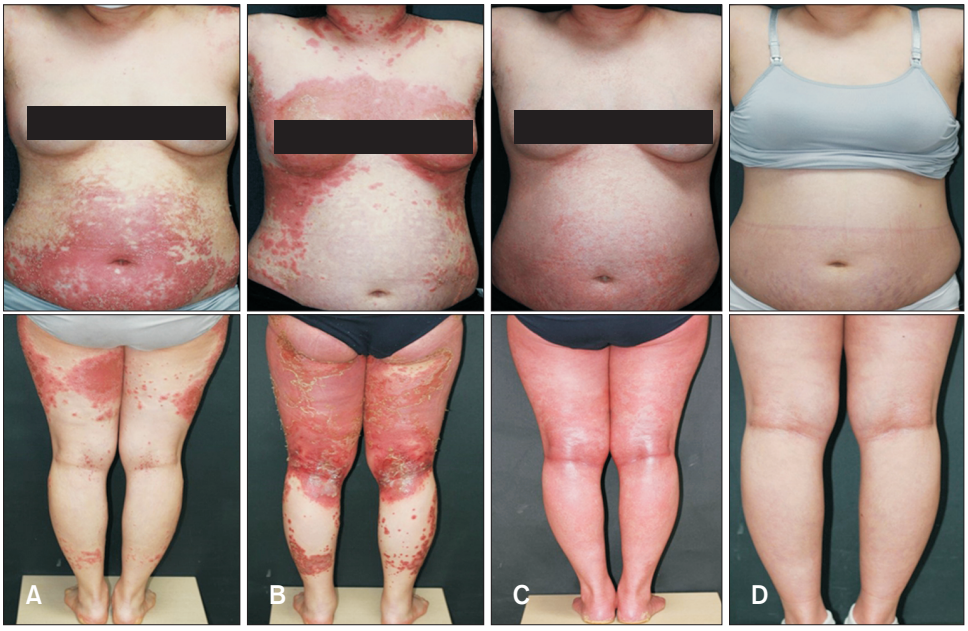

Fig. 1. Clinical presentation of generalized pustular psoriasis of pregnancy induced by hydroxychloroquine. (A) Erythematous patches and pustules on trunk and both extremities. (B) Resolved previous skin lesion on abdomen but centrifugal spreading of rashes. Erythematous confluent annular scaly plaques with pustules on both lower extremities (2 weeks after systemic steroid treatment). (C) Resolved erythematous scaly patches and pustules (2 weeks after systemic cyclosporine treatment). (D) Skin lesion has almost totally cleared at 2 weeks after delivery.

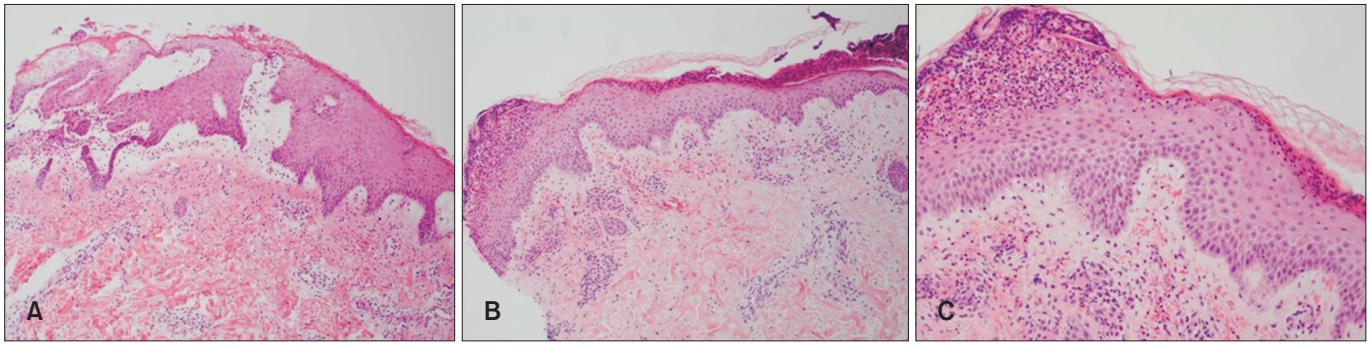

Fig. 2. (A) Subepidermal bullous lesion containing neutrophils and upper dermal neutrophilic infiltrate (H&E, ×100). (B) Subcorneal and intracorneal pustulosis. (H&E, ×100). (C) Subcorneal pustule filled with neutrophils and upper dermal neutrophilic infiltrate (H&E, ×200).

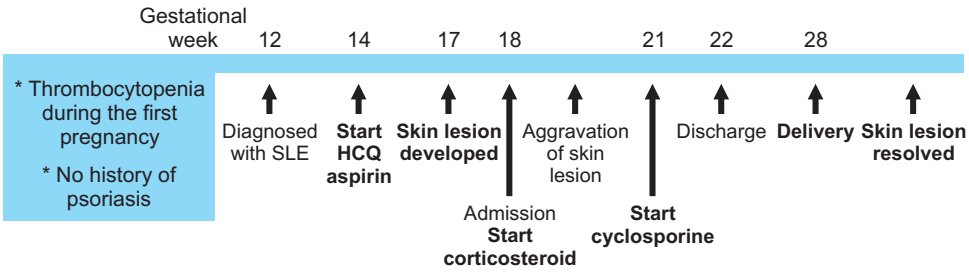

Fig. 3. The hospital course of this patient. HCQ: hydroxychloroquine.

and topical corticosteroid and anti-histamines for 2 weeks. However, the erythematous patches and pustules spread to her entire body and became annular-shaped on both legs, although the previous skin lesion improved with desquamation (Fig. 1B). Another skin biopsy from the pustules at her trunk showed subcorneal and intracorneal pustule filled with neutrophils and upper dermal neutrophilic infiltrate (Fig. 2B, C). GPPP was then diagnosed because of the biopsy result and the clinical course of the rash inconsistent with that of AGEP, which typically resolves within 15 days after discontinuation of the causative drug, with subsequent desquamation. Oral cyclosporine (2 mg/kg body weight/day) was administered while tapering off the oral corticosteroid. This resulted in remission, and she was discharged at 22 weeks' gestation (Fig. 1C).

After discharge, she had preeclampsia and an emergency caesarean section was performed at 28 gestational weeks due to fetal distress. After delivery, her skin lesion almost totally cleared except yellowish discolorations involving the nail bed (Fig. 1D). The dose of cyclosporine was then tapered and subsequently stopped. Her condition is currently controlled and she has not relapsed (Fig. 3).

DISCUSSION

GPPP, first reported as "impetigo herpetiformis" in 1872[6], is considered a rare subtype of GPP, which typically occurs during the third trimester of pregnancy. Since GPPP is considered a GPP variant, the pathogenesis of GPP may apply to GPPP patients[1]. A recent study emphasized the role of interleukin (IL)-1 and IL-36, important interleukins for neutrophil chemotaxis and pustule formation, in pustular psoriasis[7]. Tumor necrosis factor-α (TNF-α) and IL-17α were also reported as important factors for GPP pathogenesis[7]. The activities of keratinocytes, neutrophils, and monocytes were also implicated, with the inflammatory processes being driven mainly by IL-36, IL-1, or TNF-α/IL-17α[7].

GPPP is characterized by multiple sterile pustules studded on erythematous patches with systemic symptoms such as fever, fatigue, and elevated markers of inflammation including leukocytosis[1]. It usually resolves after delivery but can progress and become fatal to both mother and fetus if left untreated, as it could lead to placental insufficiency, intrauterine growth retardation, and even miscarriage[1,8]. Therefore, aggressive treatment and close monitoring are needed[1]. GPPP symptoms can usually be controlled with systemic corticosteroid, but some cases may be refractory to corticosteroid therapy[1]. Immunosuppressant including cyclosporine, anti- TNF-α drugs, and narrow-band ultraviolet B phototherapy have been used in refractory cases[1]. Labor induction should be considered when severe complications occur[2].

The etiology of GPPP and GPP remains uncertain[8]. There have been several reports of genetic mutations, especially *IL36RN* mutations, predisposing patients to developing GPP or GPPP[1,9]. Furthermore, it has been reported that *IL36RN* mutation might be associated with postpartum flare-up, but it is still unknown whether it might trigger early-onset GPPP since there have been several cases of GPPP with *IL36RN* mutation which occur during the third trimester of pregnancy[9]. However, further studies of the relationship between *IL36RN* mutations and early-onset GPPP are needed. Although the mechanism is poorly understood, hypothyroidism, hypocalcemia, infections and drugs such as *N*-butyl-scopolammonium bromide also have recently been thought to be related to GPPP onset[1,3]. In a case report of GPPP triggered by *N*-butyl-scopolammonium bromide, GPPP developed at 34 weeks' gestation after 5 days of drug ingestion[10]. However, hypocalcemia, infections, abrupt discontinuation of systemic corticosteroid, and drugs including HCQ have recently been thought to be related to GPP onset[8]. Although the mechanism of HCQ-induced GPP is not well understood, several potential mechanisms by which HCQ induces psoriatic flares have been implicated[4]. HCQ may promote IL-17 production via p38-dependent IL-23

Table 1. Reported cases of HCQ-induced new-onset generalized pustular psoriasis and generalized pustular psoriasis of pregnancy

Author	Sex/age	Diagnosis	Preceding disease for HCQ treatment	Duration of HCQ treatment	Dose of HCQ (mg/day)	Treatment after HCQ withdrawal
Friedman[13]	F/60	Generalized pustular psoriasis	Rheumatoid arthritis	3 weeks	400	None
Gravani et al.[14]	F/40	Generalized pustular psoriasis	Lichen planopilaris	1 month	400	Glucocorticoid Cyclosporine
Maglie et al.[15]	F/70	Generalized pustular psoriasis	Mixed connective tissue disorder	2 weeks	Not described	Glucocorticoid
Shindo et al.[5]	F/34	Generalized pustular psoriasis	Systemic lupus erythematosus	3 weeks	200	Glucocorticoid Granulocyte and monocyte adsorption pheresis Cyclosporine
Our case	F/33	Generalized pustular psoriasis of pregnancy	Systemic lupus erythematosus	3 weeks	200	Glucocorticoid Cyclosporine

HCQ: hydroxychloroquine, F: female.

release, thereby increasing keratinocyte growth[11]. Additionally, HCQ may interrupt cholesterol metabolism by inhibiting transglutaminase, which weakens the structural and functional integrity of the stratum corneum[12]. Moreover, an *in vitro* study demonstrated that HCQ induces hyperproliferation and irregular keratinization on cultured skin[12]. This may because HCQ, a potent epidermal transglutaminase inhibitor, causes an initial break in the barrier function of epidermis, which consequently initiates epidermal proliferation aimed at restoring the barrier function of the skin[12].

There have been five case reports of SLE, rheumatoid arthritis, and adjuvant disease inducing GPP or GPPP following the HCQ administration (Table 1)[5,13-15]. In all cases, GPP or GPPP developed 2 to 4 weeks after commencing HCQ therapy. One case improved after corticosteroid administration; three required immunosuppressant before their symptoms improved. One case improved only with the HCQ discontinuation. Our patient was refractory to corticosteroid, and systemic cyclosporine was required before her symptoms improved. Most importantly, unlike other four cases, ours is the only case of new-onset GPPP following HCQ use.

Here, GPPP developed at 17 weeks' gestation, and HCQ might have acted as a trigger factor for early-onset GPPP. However, attributing causality between the development of early-onset GPPP and HCQ use alone might be difficult, because autoimmune comorbidities including SLE may predispose individuals to psoriasis due to dysregulation of common cytokines, such as IL-17 and IL-23[4]. A recent study reported that the prevalence of psoriasis in SLE patients was found to be higher than that in the general Canadian population[16]. According to the study, psoriasis was diagnosed an average 8.8±9 years after SLE diagnosis and plaque psoriasis was the most prominent type (55/63, 87.3%)[16]. In that study, three patients had pustular-type psoriasis[16]. As GPPP developed 3 weeks after HCQ initiation and 1 month after SLE diagnosis in this case, we can speculate that HCQ might play a more important role in inducing GPPP. However, further studies of the immunologic relationship between SLE and psoriasis are needed.

In conclusion, this is the first case of early-onset GPPP following HCQ use in a SLE patient, which was maintained with systemic cyclosporine during pregnancy and completely resolved after delivery. HCQ can induce GPPP even during early pregnancy and lead to more fatal outcome for both mother and fetus if left untreated. Therefore, early-onset GPPP should be considered when administering HCQ to pregnant females.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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REFERENCES

1. Trivedi MK, Vaughn AR, Murase JE. Pustular psoriasis of pregnancy: current perspectives. Int J Womens Health 2018;10:109-115.
2. Jeong KH, Shin MK, Yang YS, Kim NI. Case report: generalized pustular psoriasis of pregnancy treated with systemic steroid and narrowband UVB. Korean J Dermatol 2008;46:1551-1555.
3. Namazi N, Dadkhahfar S. Impetigo herpetiformis: review of pathogenesis, complication, and treatment. Dermatol Res Pract 2018;2018:5801280.
4. Sachdeva M, Mufti A, Maliyar K, Lytvyn Y, Yeung J. Hydroxychloroquine effects on psoriasis: a systematic review and a cautionary note for COVID-19 treatment. J Am Acad Dermatol 2020;83:579-586.
5. Shindo E, Shikano K, Kawazoe M, Yamamoto T, Kusunoki N, Hashimoto Y, et al. A case of generalized pustular psoriasis caused by hydroxychloroquine in a patient with systemic lupus erythematosus. Lupus 2019;28:1017-1020.
6. Von Hebra F. Ueber einzelne während schwangerschaft, des wochenbettes und bei uterinalkrankheiten der frauen zu beobachtende hautkrankheiten. Wien Med Wochenschr 1872;22:1197-1202. German.
7. Johnston A, Xing X, Wolterink L, Barnes DH, Yin Z, Reingold L, et al. IL-1 and IL-36 are dominant cytokines in generalized pustular psoriasis. J Allergy Clin Immunol 2017;140:109-120.
8. Hoegler KM, John AM, Handler MZ, Schwartz RA. Generalized pustular psoriasis: a review and update on treatment. J Eur Acad Dermatol Venereol 2018;32:1645-1651.
9. Yoshikawa M, Rokunohe D, Kimura A, Takahashi M, Korekawa A, Nakajima K, et al. Significance of IL36RN mutation analyses in the management of impetigo herpetiformis: a case report and review of published cases. J Dermatol 2021;48:699-702.
10. Guerriero C, Lanza Silveri S, Sisto T, Rosati D, De Simone C, Fossati B, et al. Impetigo herpetiformis occurring during N-butyl-scopolammonium bromide therapy in pregnancy: case report. J Biol Regul Homeost Agents 2008;22:141-144.
11. Said A, Bock S, Lajqi T, Müller G, Weindl G. Chloroquine promotes IL-17 production by CD4+ T cells via p38-dependent IL-23 release by monocyte-derived Langerhans-like cells. J Immunol 2014;193:6135-6143.
12. Wolf R, Schiavo AL, Lombardi ML, de Angelis F, Ruocco V. The in vitro effect of hydroxychloroquine on skin morphology in psoriasis. Int J Dermatol 1999;38:154-157.
13. Friedman SJ. Pustular psoriasis associated with hydroxychloroquine. J Am Acad Dermatol 1987;16:1256-1257.
14. Gravani A, Gaitanis G, Zioga A, Bassukas ID. Synthetic antimalarial drugs and the triggering of psoriasis - do we need disease-specific guidelines for the management of patients with psoriasis at risk of malaria? Int J Dermatol 2014;53:327-330.
15. Maglie R, Dini V, Romanelli M. Pustular psoriasis induced by hydroxychloroquine: a case report to confirm a rare association. J Am Acad Dermatol 2016;74(5 Suppl):AB265.
16. Tselios K, Yap KS, Pakchotanon R, Polachek A, Su J, Urowitz MB, et al. Psoriasis in systemic lupus erythematosus: a single-center experience. Clin Rheumatol 2017;36:879-884. Erratum in: Clin Rheumatol 2019;38:269.