# รายงานผู้ป่วยและทบทวนวรรณกรรม ในผู้ป่วยที่เกิดผื่นแพ้ยาแบบ acute Generalized Exanthematous Pustulosis ภายหลังได้รับยาฟาวิพิราเวียร์ เพื่อรักษาโรคปอดอักเสบจากการติดเชื้อไวรัสโคโรนา 2019

# Acute Generalized Exanthematous Pustulosis After the First Dose of Favipiravir in a Patient with COVID-19 Pneumonia: A Case Report and Literature Review


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## บทคัดย่อ

ผู้ป่วยชายอายุ 47 ปี ได้รับการส่งตัวมารักษาต่อ ณ โรงพยาบาลแห่งหนึ่ง เนื่องจากโรคปอดอักเสบจากการติดเชื้อไวรัสโคโรนา 2019 ภายหลังจากได้รับยาฟาวิพิราเวียร์ครั้งแรก ผู้ป่วยเกิดผื่นชนิดมีตุ่มหนองกระจายทั่วบริเวณลำตัว แขน และขา โดยตรวจไม่พบว่ามีสาเหตุจากการติดเชื้ออื่น จึงได้รับการวินิจฉัยว่าเป็นผื่นแพ้ยาชนิด acute generalized exanthematous pustulosis (AGEP) การรักษาได้แก่ การหยุดยาฟาวิพิราเวียร์ที่คาดว่าจะเป็นสาเหตุ การให้ยาสเตียรอยด์แบบกินและแบบทา ผู้ป่วยอาการดีขึ้นภายใน 3 วันหลังการรักษา ยาฟาวิพิราเวียร์ซึ่งเป็นยาใหม่ที่ได้นำมาใช้ในการใช้ในการรักษาการติดเชื้อไวรัสโคโรนา 2019 ในประเทศไทย พบการแพ้ยาแบบผื่นได้น้อย ความสัมพันธ์ระหว่างยาฟาวิพิราเวียร์กับผื่นแพ้ยารุนแรงชนิด AGEP ยังไม่ชัดเจน รายงานผู้ป่วยฉบับนี้มีวัตถุประสงค์เพื่อรายงานการเกิดผื่นแพ้ยาชนิดรุนแรงจากยาฟาวิพิราเวียร์



**คำสำคัญ:** ผื่นแพ้ยา, โรคติดเชื้อไวรัสโคโรนา 2019

ABSTRACT

A 47-year-old man was referred to a hospital for treatment of coronavirus disease 2019 (COVID-19) pneumonia and developed progressive generalized pustular skin lesions over entire trunk, back and both upper extremities after the first dose of oral favipiravir for the treatment of his condition. No infectious causes of pustular lesions were identified upon investigations, and the diagnosis of acute generalized exanthematous pustulosis (AGEP) was made. With the prompt withdrawal of favipiravir, along with the initiation of systemic and topical corticosteroid treatment, his skin lesions resolved with desquamation and erythema within 3 days. Dermatologic adverse reactions from favipiravir, the novel antiviral agent for the treatment of SARS-COV2 infection, are uncommon. The association of favipiravir and acute generalized exanthematous pustulosis (AGEP), a severe form of skin reaction, remains unclear. We reported a case of patient who developed AGEP with the oral favipiravir as the causative agent.

**Key words:** acute generalized exanthematous pustulosis, AGEP, COVID-19

## Background

Acute generalized exanthematous pustulosis (AGEP) is a serious cutaneous adverse reaction manifested by the rapid eruption and dissemination of sterile, non-follicular pustules on edematous erythema. Most cases of AGEP are attributed to medications, particularly antimicrobial agents, while a minority are associated with viral infections, such as cytomegalovirus or parvovirus B19 infection. The distribution of the skin lesions favors trunk, proximal extremities, and intertriginous areas. The lesions usually develop within 24-48 hours after initiating the offending medication (Szatkowski & Schwartz, 2015). However, cutaneous manifestations after receiving treatment of coronavirus disease 2019 (COVID-19) characterized by AGEP has not been reported (Suchonwanit *et al.*, 2020).

## Case presentation

A 47-year-old Asian man presented in August 2021 with low-grade fever, generalized myalgia, and dry cough for 1 week. His medical history included controlled type 2 diabetes mellitus and hyperlipidemia. He had been taking metformin, glipizide, and simvastatin for eight years. He denied using any of over-the-counter drugs, illicit drugs, supplements, or herbs. He had no previous history or family history of dermatologic diseases and also denied any history of drug or food allergies. Additionally, he had not received COVID-19 vaccination.

During physical examination, he showed tachypnea with a respiratory rate of 30 breaths per minute and oxygen saturation of 92% at room air. A nasal swab RT-PCR confirmed COVID-19 infection. His chest radiograph demonstrated bilateral lower lung ground-glass opacities. He was admitted at community hospital for treatment of COVID-19 pneumonia and received high-flow nasal cannula therapy to alleviate dyspnea. Medications including favipiravir 900 mg. and intravenous methylprednisolone (IVMP) 250 mg. were initiated upon admission. Subcutaneous enoxaparin 40 mg. was also started for thromboprophylaxis.

Six hours after taking the medications, the patient developed pruritic erythematous macules and patches topped with pustules, which progressed to cover his entire back, trunk, arms, and thighs within two days. Oral favipiravir was continued at a dosage of 900 mg twice daily on the first day and subsequently 400 mg twice daily for a total of five days. IVMP was administered for three days and then switched to oral dexamethasone 10 mg daily. On day 5 of admission, his chest radiograph showed progression of pneumonia, prompting his referral to our center for intensive care.

During physical examination at our center, his body temperature was 38.3 C°. Cutaneous examination revealed generalized superficial pinpoint, non-follicular pustules on various sizes of erythematous macules and patches, concentrated on the back, trunk, arms, and thighs, which were typically compatible with AGEP. (Figure 1A-B) No mucosal lesion were identified in this patient.

Due to the lack of histological diagnosis, we implemented the validated diagnostic score from the EuroSCAR study in this patient (Sidoroff *et al*., 2007). The total score was 8, accounting for typical sterile pustular lesions and erythema, a compatible rash distribution, post-pustular desquamation, fever >38C°, and PMN >7,000/$mm^3$, thus interpreted as probable AGEP. Generalized pustular psoriasis was considered in the differential diagnosis, but his medical history, including that of his family members, did not suggested this condition.

We also considered a direct association between COVID-19 infection and AGEP as a differential diagnosis. However, the obvious temporal relationship between the initiation of favipiravir and the development of AGEP, along with the progression of the lesions despite treatment for COVID-19 infection with antiviral and corticosteroids, suggested that the most likely etiology of AGEP in this patient is from favipiravir.

Initial complete blood count results showed a hemoglobin of 10.9 g/dL, WBC 9,970 cells/cu.mm (neutrophils 80.1%, eosinophils 0.4%, and lymphocytes 13.8%), and platelets 306,000 cells/cu.mm. The erythrocyte sedimentation rate was 50 mm/hr and high-sensitivity C-reactive protein was 112.6 mg/L. Anti-HIV testing was negative, and other laboratory results were unremarkable. Skin scrapping for gram stain, KOH preparation, and culture were negative, and skin biopsy was not performed with the patient's agreement.

The antiviral treatment was therefore switched from favipiravir to intravenous

remdesivir (200 mg loading dose, and then 100 mg once daily) for 5 days. IVMP 250 mg daily was restarted for treatment of severe COVID-19 pneumonia. AGEP was managed with 0.1% topical triamcinolone acetonide cream.

## Outcome & Follow-up

The pustular lesions gradually resolved with desquamation within 3 days after supportive treatment and discontinuation of favipiravir (Figure 1C-D). Systemic corticosteroids were subsequently changed to oral dexamethasone with the plan to gradually taper off within 4 weeks. However, the erythema persisted throughout the course of treatment for COVID-19 pneumonia. The patient decided to follow-up on his skin lesion with a physician at the community hospital.

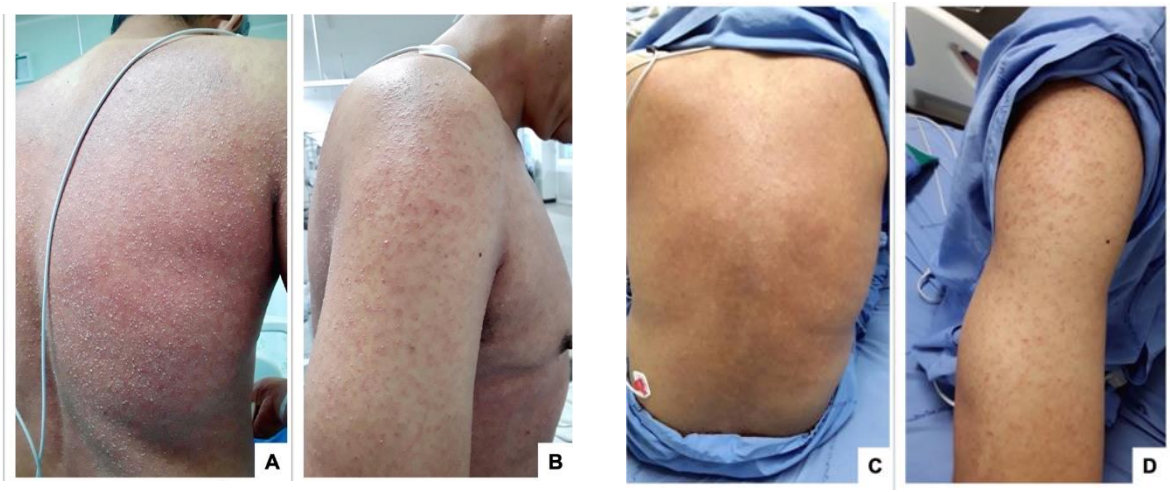


**Figure 1** A and B demonstrated acute generalized exanthematous pustulosis (AGEP) after initiation of favipiravir on the trunk and arms. C and D showed skin manifestation 3 days after discontinuation of favipiravir.

## Case Discussion

COVID-19 or SARS-CoV2 infection is currently one of worldwide health problems, and numerous therapeutic agents are vigorously implemented for the treatment. There have been several reports related to the cutaneous manifestations of COVID-19. Among these lesions, AGEP is considered a serious adverse event of COVID-19-infected patients, with most cases being attributed to medications. Several reports have demonstrated the association of AGEP with treatments of COVID-19 including hydroxychloroquine, anti-malarial agent, cephalosporin, azithromycin, and lopinavir/ritonavir (Alzahrani et al., 2020; Haraszti, et al., 2020; Najar Nobari et al., 2021; Pezzarossa et al., 2021). Notably, there was also a reported case of AGEP in COVID-19 with multiorgan dysfunction without any identifiable causative agents (Ordoñez *et al*., 2021). The reports of AGEP in COVID-19 patients are summarized in table 1.

Favipiravir, a purine nucleoside analogue, has antiviral activity against SARS-CoV2 via competitive inhibition of viral RNA-dependent RNA polymerase (Agrawal et al., 2020). In Thailand, favipiravir has been approved for the treatment of COVID-19 infection. (Department of Medical Services, 2564) A systematic review and metanalysis has shown promising efficacy for clinical and laboratory improvement with well-tolerated side effects (Shrestha et al., 2020). Regarding the analysis of adverse drug events from the World Health Organization (WHO) database, favipiravir-associated skin and soft tissue adverse reactions are relatively uncommon, with only 0.5-1% of cutaneous hypersensitivity reactions such as rash or pruritus (Kaur *et al*., 2020). We presented an unusual case of cutaneous reaction within 6 hours after the first dose of favipiravir, which progressively involved a large body surface area within 2 days after initiating treatment and resolved after discontinuation of the medication. Although a case of Favipiravir-associated AGEP has been reported, the onset of AGEP occurred 16 days after the administration of medication (Atak et al., 2021) as shown in Table 1.

Symptoms of AGEP generally improve within several days after the removal of the causative medication. Supportive care with topical moisturizers, topical steroids, and oral antihistamines ameliorates the symptoms. Fluid and electrolyte replacement and systemic corticosteroids may be used in severe cases. Other immunosuppressive agents may be warranted in severe cases that are not responsive to systemic corticosteroid (De et al., 2018; Hadavand, *et al*., 2020).

## Conclusion and Suggestion

We have detailed a potential severe cutaneous side effect associated with favipiravir, an antiviral treatment for COVID-19. Prompt discontinuation of the offending medications is the mainstay AGEP treatment, complemented by topical corticosteroid and supportive care.

## Ethical Considerations

The written informed consent for publication of this case report and accompanying images was obtained from the patient. The protocol was reviewed and approved by the Research Ethics Committee of Faculty of Medicine, Chiang Mai University (Research ID: 8406/ Study Code MED-2564-08406).

## Contributions

Chalermkiat Kansuttiviwat contributed to obtaining patient consent, performing data collection, literature review, and writing first draft of manuscript. Pattraporn Tajarernmuang coordinated the project and writing the manuscript. Napatra Tovanabutra contributed to describing the skin lesion, confirming the diagnosis, and writing the manuscript. All authors reviewed and edited the manuscript and approved the final manuscript. Konlawij Trongtrakul helped writing the manuscript. Warawut Chiawong helped writing the manuscript and submitting the manuscript to the journal.

**Table 1** Previous reports of acute generalized exanthematous pustulosis in COVID-19 patients

| Patient | Age / sex | Comorbidities | Suspected causative agent | Date onset of AGEP | treatment | Outcome | Ref. |
|---|---|---|---|---|---|---|---|
| 1 | 47 / male | Diabetes mellitus, dyslipidemia | Favipiravir | 6 hours after favipiravir initiation | IVMP 250 mg daily, and 0.1% topical TA | Progressive improvement of skin lesions within 3 days after favipiravir discontinuation | - |
| 2 | 78 / male | BPH, coronary artery disease and atrial fibrillation | Cefepime | 7 days after cefepime initiation | Topical emollient | Resolution of exanthem within few days with post-pustular desquamation | (Haraszti, *et al.*, 2020) |
| 3 | 34 / male | - | Azithromycin, HCQ, lopinavir/ritonavir, oseltamivir, ceftriaxone, clindamycin, ceftazidime | Not reported | Betamethasone valerate 0.1% ointment and lotion | The pustular rash not improving upon discharge | (Alzahrani *et al.*, 2020) |
| 4 | 44 / female | Hypertension, dyslipidemia, obesity | No identifiable causative medications | At the onset of hospital admission | Vancomycin, piperacillin-tazobactam, and clindamycin for septic shock, high-dose vasopressor, corticosteroids | Progressive improvement of skin lesions (The duration of treatment is not reported) | (Ordonez *et al.*, 2021) |
| 5 | 20 / male | Not reported | Favipiravir | 16 days after favipiravir initiation | Oral prednisolone 1 mg/kg/d | Resolution with desquamation within 7 days after treatment | (Atak *et al.*, 2021) |

Abbreviations: AGEP = Acute Generalized Exanthematous Pustulosis, BPH = Benign prostatic hyperplasia, HCQ = Hydroxychloroquine, IVMP = Intravenous Methylprednisolone, SJS = Stevens-Johnsons Syndrome, TA = Triamcinolone acetonide

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