

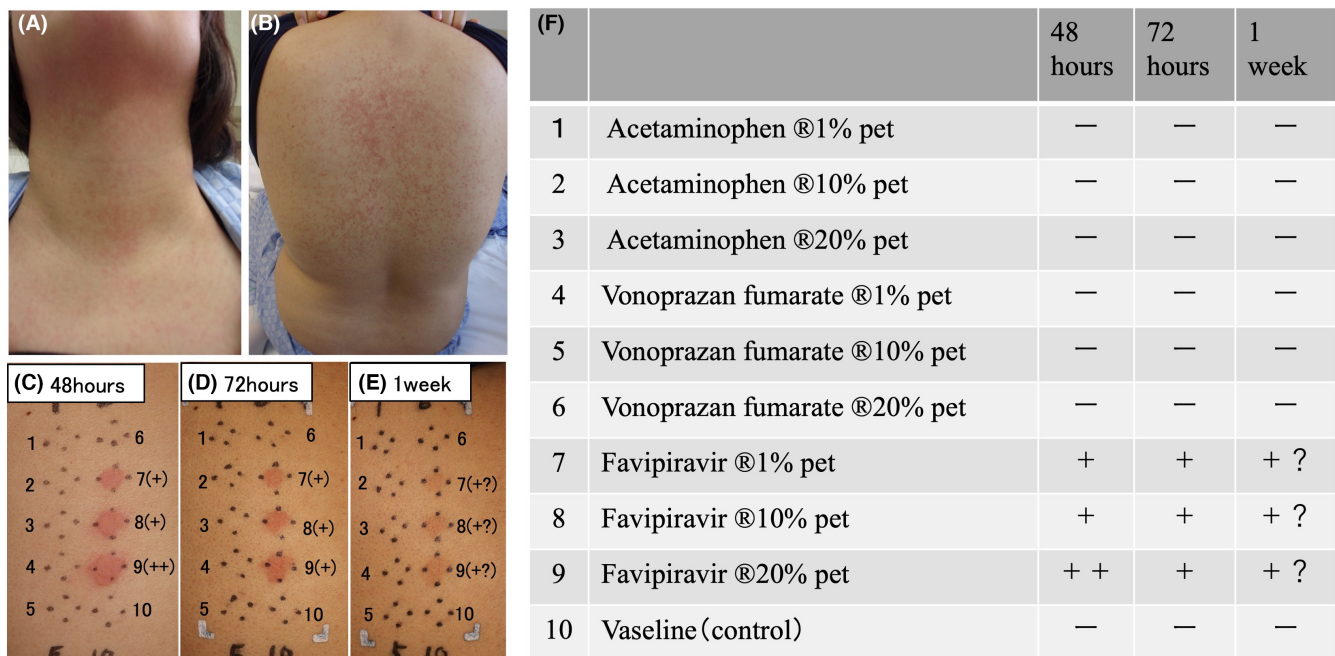
## CORRESPONDENCE

# A case of disseminated erythematous drug eruption caused by favipiravir in a patient with COVID-19

Favipiravir is an RNA-dependent RNA polymerase inhibitor that was developed as a therapeutic agent for novel or reemerging influenza infections. It is also used to treat COVID-19,<sup>1</sup> which is currently rampant throughout the world. We herein report a case of disseminated erythematous drug eruption due to favipiravir diagnosed from the results of a drug-induced lymphocyte transformation test (LTT) and patch tests.

A 42-year-old Japanese woman with no previous history of drug eruption was admitted to the department of respiratory medicine for pneumonia and liver dysfunction due to COVID-19 and began treatment with favipiravir. She was referred to our department following

an itchy eruption, which had appeared 12 days after taking the drug (19th day after the onset of infection). When she first visited our department, the patient presented with a maculopapular rash without any mucosal lesions, which was observed on the whole body and the face (Figure 1). Laboratory findings showed aspartate aminotransferase 31 U/L (normal range 13–30 U/L), alanine aminotransferase 64 U/L (7–23 U/L), lactate dehydrogenase 260 U/L (124–222 U/L), and C-reactive protein 2.92 mg/dL (0.3 mg/dL). Taking viral toxic eruption or drug eruption into consideration, we stopped all oral medicine given after admission, and the administration of oral antiallergic agents was started. After the eruption and infection had healed, patch tests



**FIGURE 1** (A, B) Widespread disseminated erythema was found on the trunk / neck with pruritus. (C–F) The results of the path tests. Favipiravir showed positive results at all concentrations and judgment dates (arrows), according to the criteria of the international contact dermatitis research group. The reagents used were, vertically from the upper left: (1) acetaminophen 1% pet, (2) acetaminophen 10% pet, (3) acetaminophen 20% pet, (4) vonoprazan fumarate 1% pet, and (5) vonoprazan fumarate 10% pet. And from the upper right: (6) vonoprazan fumarate 20% pet, (7) favipiravir 1% pet, (8) favipiravir 10% pet, (9) favipiravir 20% pet, and (10) Vaseline (control). (C) favipiravir 1% and 10% pet showed ++, and 20% pet showed + at 48 h. (D) favipiravir 1%, 10%, and 20% pet showed + at 72 h. (E) favipiravir 1%, 10%, and 20% pet showed + ? at 1 week.

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and LTT were performed. The patient received six oral medications during hospitalization, but based on the duration of administration and previous reports, we narrowed the list of potentially responsible drugs to three. The LTT, which was performed on the 43rd day after the onset of infection, results were positive for all three drugs, acetaminophen 520% (S.I. 5.2), vonoprazan fumarate 280% (S.I. 2.8), and favipiravir 3730% (S.I. 37.3). When the patch tests were performed at 1%, 10%, and 20% concentrations, favipiravir showed positive results at all concentrations for 48h, 72h, and 1 week, respectively. On the contrary, acetaminophen and vonoprazan fumarate were all negative (Figure.1). Based on the above results, our patient was diagnosed as having favipiravir-induced disseminated erythematous drug eruption. To confirm, a patch test for favipiravir was performed on three healthy volunteers all of which were negative.

The frequency of cutaneous manifestation in COVID-19 has been reported to be 1%–20%.<sup>2,3</sup> Clinically, the frequency of patchy erythema, chilblain-like rash, and urticaria-like erythema is high.<sup>3,4</sup> In addition, the eruption typically occurs around 10 days after onset of infection.<sup>4</sup> In our case, the appearance of the rash was a little delayed, but it was clinically consistent with the rash caused by COVID-19; thus, we examined whether the course of the toxicoderma was a virus or a reaction to the patient's medication. Unfortunately, the biopsy was not performed; however, based on the patch tests and LTT results, we diagnosed our patient as having a favipiravir-induced disseminated erythematous drug eruption. Favipiravir rarely causes skin disorders, and seven cases of drug eruption have previously been reported as follows: three with maculopapular rash, two with urticarial rash, and one with Stevens-Johnson syndrome.<sup>5–7</sup> To the best of our knowledge, this is the first report of positive patch tests leading to a definitive diagnosis. Since multiple drugs are used for COVID-19 patients, the possibility of drug eruption must be considered when diagnosing a rash.

#### CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

#### DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

#### ETHICS STATEMENT


Approval of the research protocol: The case report has been approved at this facility.

Informed consent: Patient consent was obtained using the institutional patient consent form, which includes permission for social media publication.

Registry and the Registration No. of the study/trial: Not applicable.

Animal Studies: Not applicable.

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