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Acute generalized exanthematous pustulosis following treatment with favipiravir in a patient with COVID-19 without hydroxychloroquine use: Report of the first case

Dear Editor,

Favipiravir is an antiviral agent used in the treatment of COVID-19 infection, and related cutaneous adverse events are rare.[1] Acute generalized exanthematous pustulosis (AGEP) has been reported in COVID-19 patients, mostly associated with hydroxychloroquine (HCQ). There are few AGEP cases in COVID-19 patients reported due to β-lactam antibiotics [2,3] in the literature. Herein, we report the first case of favipiravir-induced AGEP with histologic findings.

A 20-year-old male was admitted for a rapid onset, mildly itching eruption for two days. Physical examination revealed diffuse erythematous, edematous plaques involving the trunks and proximal extremities with grouped pustular lesions on an edematous-erythematous background (Figure 1A–C). During admission, body temperature was 38.7°C, and other vital signs were normal. The patient was hospitalized for COVID-19 infection 16 days ago, where he presented with generalized malaise, fatigue, and myalgia. After the

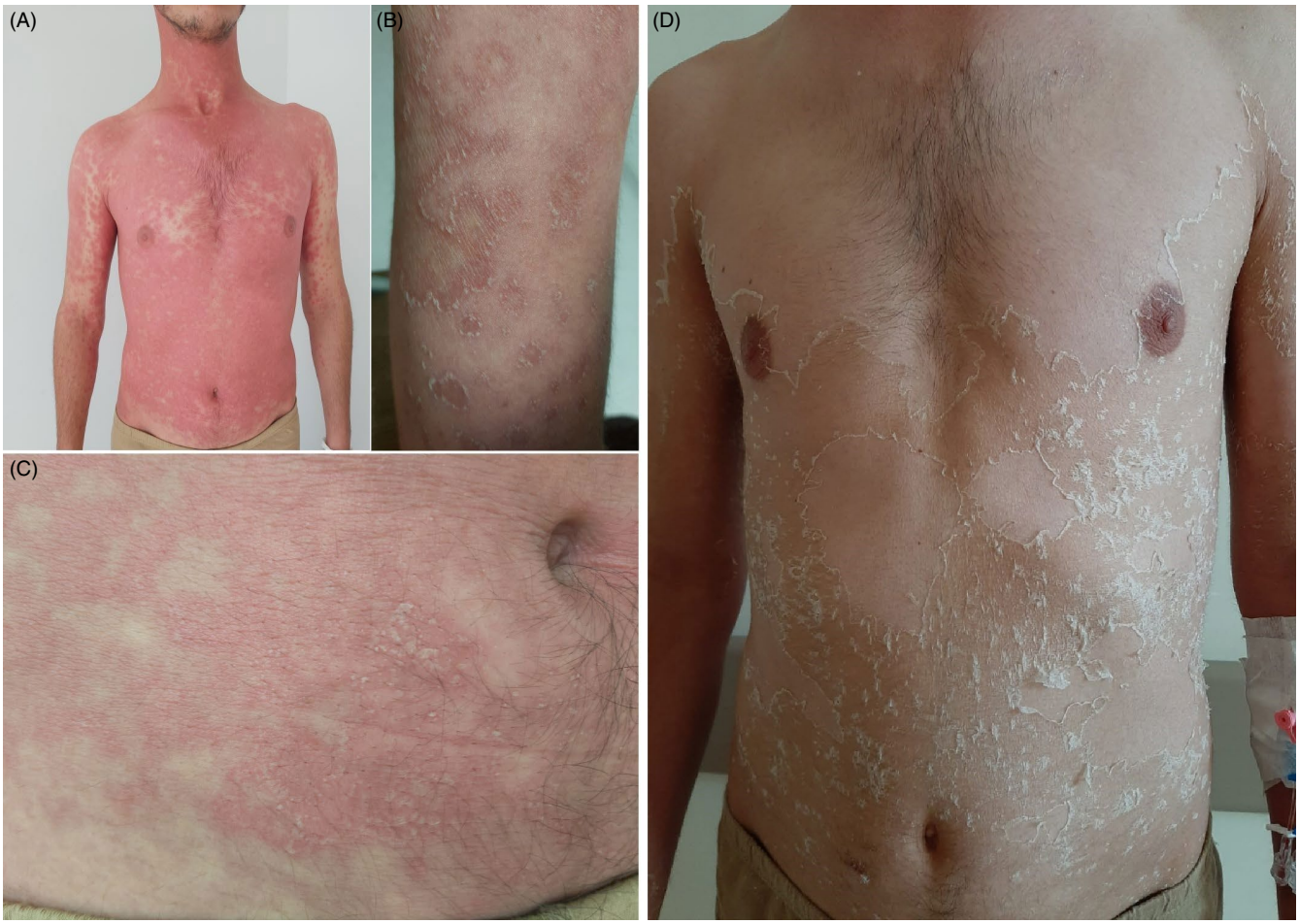

FIGURE 1 Clinical images of the patient at the time of presentation. (A) Diffuse erythematous, edematous plaques involving the trunks and proximal extremities. (B) Annular, erythematous plaques with polycyclic contours and superficial pustule lakes on the forearm. (C) Close image of the abdominal lesions showing polycyclic plaques and grouped pustular lesions along the borders of the lesion. (D) Widespread desquamation of the skin after the treatment on day 8

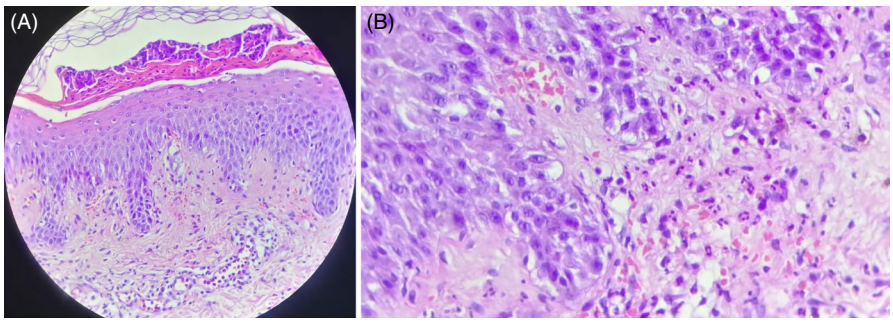

FIGURE 2 Histopathologic images of the skin biopsy obtained from the abdominal lesion, where the pustules were present. (A) Acanthosis of the epidermis with numerous neutrophilic subcorneal/intracorneal spongiotic pustules with papillary dermal edema. Mixed inflammatory infiltrate composed of lymphocytes, neutrophils, and rare eosinophils in the dermis (H&E ×10). (B) Higher magnification of the dermo-epidermal junction shows abundant eosinophilic infiltrate in the papillary dermis (H&E ×20).

diagnosis of COVID-19 infection, favipiravir monotherapy has been started with a loading dose of 1600 mg bid, followed by 600 mg bid daily for 7 days. His symptoms resolved completely after the treatment. Medical records showed that our patient did not take any drugs other than favipiravir in the last 8 weeks and the patient denied any medication intake in the last 8 weeks including over the counter medications. The patient's past medical history and family history was insignificant, and he did not report any skin conditions. Laboratory tests showed neutrophilic leukocytosis (white blood cell count: 20 390/mm3, neutrophil count: 16 620/mm^3). Blood, urine, and pustule cultures were negative for bacteria. Hepatitis panel, VDRL, and HIV studies were negative. Skin biopsy was obtained from the abdominal lesions with differential diagnoses including viral exanthema, AGEP, subcorneal pustular dermatosis, and psoriasis. Histologic examination showed acanthosis of the epidermis with numerous neutrophilic subcorneal/intracorneal spongiotic pustules with papillary dermal edema. There was mixed inflammatory infiltrate composed of lymphocytes, neutrophils, and rare eosinophils in the dermis (Figure 2A–B). The patient has been diagnosed with favipiravir-induced AGEP, and 1 mg/kg/day systemic prednisolone treatment was initiated. The lesions resolved with desquamation after 7 days with oral methylprednisolone treatment (Figure 1D).

Favipiravir is a purine nucleoside analogue and competitive inhibitor of viral RNA-dependent RNA polymerase with antiviral activity against influenza A and B viruses and SARS-CoV-2 virus. Favipiravir and/or HCQ combination has been approved as first-line treatment options in COVID-19 positive patients. A recent study showed the efficacy of favipiravir in COVID-19 patients leading to significant clinical and laboratory improvements with no serious adverse events.[4] Favipiravir-related cutaneous adverse events are rare, reported as pruritus and eczema <0.5% of the patients, and no AGEP cases reported to date.[1]

COVID-19 related symptoms reported synchronously with virus-related systemic symptoms, whereas drug adverse reactions likely arise within few hours to days after the treatment.[5] In AGEP, the average duration of drug exposure before onset of the symptoms depends on the causative drug. Antibiotics typically have short latency period of 24–72 hours, whereas other drugs such as HCQ are often associated with longer latency periods usually around 10–12 days.[6] Delayed presentation (after 7 days) in cefepime secondary AGEP in a case of COVID-19 patient has been reported.[2] Our case has presented with AGEP 16 days after treatment which was a longer latency period compared to AGEP reported in COVID-19 infected patients in the recent literature. We hypothesize that combination of favipiravir and genetic disposition with COVID-19 induced cytokine storm led to delayed development of AGEP in our case.[7] The limitation of our case study is that we were not able to perform patch testing to confirm favipiravir as inciting agent. The current clinical presentation might have been triggered with COVID-19 infection itself, as well. Further reports will confirm our findings.

We aim to emphasize an unreported possible side effect of this new agent which has become widely used during pandemic, and when dealing with skin findings, favipiravir should be kept in mind as a causative agent.

INFORMED CONSENT

INFORMED CONSENT WAS OBTAINED.KEYWORDS

acute generalized exanthematous pustulosis, AGEP, COVID-19, cutaneous adverse event, favipiravir

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Not available.

CONFLICT OF INTEREST

Dr. Babar K. Rao is a consultant for Caliber ID (The manufacturer of VivaScope). The other authors have no conflict of interest to declare.

ETHICAL APPROVAL

The patient in this manuscript have given written informed consent to the publication of his case details.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article.

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