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Case Report

A case of COVID-19 diagnosed with favipiravir-induced drug fever based on a positive drug-induced lymphocyte stimulation test

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ABSTRACT

As of October 2020, there is still no specific drug to treat COVID-19 as it rages worldwide. Favipiravir, indicated for the treatment of new and re-emerging influenza infections, has been suggested to be effective against SARS-CoV-2, although this is not yet fully validated. We administered favipiravir to a 64-year-old female patient with COVID-19. Her symptoms resolved quickly after the start of treatment, with reduction of SARS-CoV-2 viral load, but she developed a fever again on day 12. Since the fever was relieved by discontinuation of favipiravir, and based on positive results with a drug-induced lymphocyte stimulation test, we diagnosed her with favipiravir-induced drug fever. A decrease in the serum concentration of favipiravir was observed along with resolution of the fever. The present case suggests that drug fever should be considered in the differential diagnosis of relapsing fever episodes in COVID-19 patients receiving favipiravir.

Introduction

COVID-19 has been spreading around the world since 2019, and Japan is no exception. COVID-19 is characterized by a wide variety of clinical presentations, with some cases remaining asymptomatic and others progressing to fatal pneumonia (Huang et al., 2020).

As of October 2020, the only drugs approved for COVID-19 in Japan are remdesivir and dexamethasone, both of which have been reported to be effective (Horby et al., 2021; Beigel et al., 2020). Favipiravir, which was developed in Japan and is indicated for the treatment of new and re-emerging influenza infections, is undergoing clinical trial for efficacy in COVID-19.

The common side effects of favipiravir include hyperuricemia, diarrhea and neutropenia, along with a few reports of drug fever. We experienced a patient with COVID-19 who had a fever during the administration of favipiravir and was diagnosed with favipiravir-induced drug fever based on the positive result of a drug-induced lymphocyte stimulation test.

Case report

The patient was a 64-year-old woman who presented with fatigue, joint pain and loss of appetite. She was admitted to the hospital for treatment of COVID-19 after testing positive on the SARS-CoV-2 antigen test. When she came to the hospital, she reported having had a persistent fever for approximately 1 week.

Her vital signs on admission were: blood pressure, 121/89 mmHg; heart rate, 84 beats per minute; body temperature, 36.9 °C; respiratory rate, 18 breaths per minute; and arterial oxygen saturation, 94% (room air). Blood tests showed normal total white blood cell (WBC) and absolute lymphocyte counts, elevated C-reactive protein (CRP) levels, and high lactate dehydrogenase (LDH) levels (WBC count: 5,200 per μL [Neutrophil 69.7%, Lymphocyte 24.0%; 1248 per μL], CRP: 3.30 mg per dL, and LDH: 280 U per L). Her chest

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computed tomography (CT) showed extensive ground-glass opacity in both lungs.

After admission, favipiravir (3600 mg per day on the first day and 1600 mg per day thereafter) was started on day 1 (Figure 1). SARS-CoV-2 quantitative reverse transcription-polymerase chain reaction (RT-qPCR) of nasopharyngeal swabs just before the administration of favipiravir indicated a SARS-CoV-2 RNA viral load of 2.64×10^5 copies per μL (Sakamaki et al., 2020; Kawasuji et al., 2020). She had a fever of 38 °C on day 2, and oxygen was started on day 3; by day 6, she had improvement in the fever and other symptoms. Therefore, we considered that COVID-19 was in remission.

However, on day 12, the patient again developed a fever of 38 °C, thought to be caused by bacterial pneumonia or drug fever related to favipiravir. Her respiratory condition was good, and supplemental oxygen was discontinued on day 12. There were no findings of lung crackles, abdominal irritation, skin phlebitis/cellulitis or sinusitis in the physical examination. Blood tests showed no evidence suggestive of bacterial pneumonia, and severe anemia and elevated bilirubin were not observed. The uric acid level was high at 10.6 mg per dL, but suspected clinical symptoms of gout, such as swelling of the joints, were not observed. Chest radiographs and blood tests were taken, but there were no signs of pneumonia and blood cultures were negative. Urine culture was not performed because there were no complaints of bladder irritation suggesting bacterial urinary tract infection. Favipiravir was discontinued on day 13 because there were few subjective COVID-19 symptoms other than fever, and a decreased viral load from nasopharyngeal swab collected on day 9 was revealed on day 12, and a strong suspicion emerged of drug fever caused by favipiravir. There was, however, no new skin rash that was suspicious of a drug eruption.

After the discontinuation of favipiravir, the patient's body temperature gradually decreased, there was no worsening of symptoms, and her fever was relieved without antimicrobial therapy. The SARS-CoV-2 viral load of nasopharyngeal swabs on day 16 had decreased to 5.17×10^2 copies per μL, which is unlikely to represent a worsening of COVID-19. The patient was discharged from the hospital on day 17, and after obtaining informed consent, a drug-induced lymphocyte stimulation test (DLST) of her serum was performed at discharge, which was positive for favipiravir with a stimulation index (SI) of 2.2 (cut-off value, 2.0).

We measured the patient's favipiravir blood concentration as part of exploratory, exhaustive factor analysis for drug fever caused by favipiravir, revealing serum favipiravir concentrations of 62.80 mg per L, 67.23 mg per L, 73.92 mg per L and 0.15 mg per L approximately 3 h after drug administration on days 6, 9, 13 and 15, respectively.

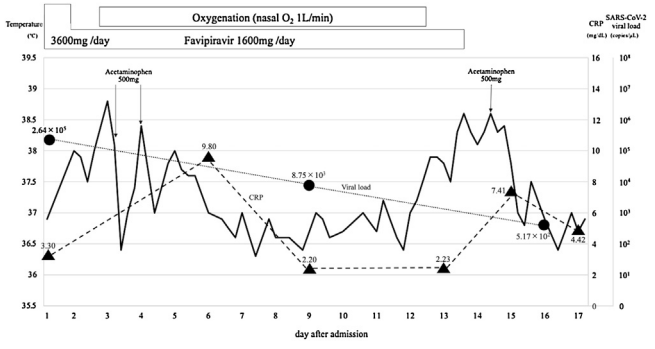

Figure 1. The clinical course of the patient.

Discussion

Favipiravir (AVIGAN®) prevents viral replication by selectively inhibiting RNA polymerase, which is used for gene replication in RNA virus cells (Shannon et al., 2020). It is effective against all human A, B and C influenza viruses, including neuraminidase inhibitor-resistant viruses. Favipiravir shows moderate antiviral activity in vitro against SARS-CoV-2, a type of RNA virus, and is expected to be a therapeutic agent for COVID-19 (Dauby et al., 2021).

The dosing protocol for favipiravir in COVID-19 is 1800 mg twice a day on day 1 and 800 mg twice a day on day 2 and thereafter for 10 days (maximum 14 days). Although favipiravir has been shown to be safe in various studies, the risks of teratogenicity, QT prolongation, and hyperuricemia need to be considered (Pilkington et al., 2020). Elevated blood uric acid levels are a frequent side effect of favipiravir; however, levels normalize quickly after discontinuation of favipiravir, and few hyperuricemia symptoms were observed in most studies (Mishima et al., 2020). Case reports of drug fever with favipiravir, as experienced in the present case, are still few.

Drug fever is the febrile response to a drug without cutaneous manifestations (Johnson and Cunha, 1996). Although the mechanisms of drug fever are diverse, the positive DLST in our patient revealed that the drug fever, in this case, was caused by type intravenous hypersensitivity. DLST is the most commonly used in vitro test to detect the causative agent of drug allergy and assesses the proliferation of lymphocytes sensitized by the antigenic stimulus of a drug (Saito et al., 2008). However, DLST does not have high sensitivity and specificity, and it is not used as a definitive diagnostic test of drug fever but is instead used as a reference value. Also, the SI that should be considered indicative of sensitization is rather controversial because it depends on various factors. In general, we use an SI of >2 to classify the test as positive, based on negative values in exposed, but not allergic, individuals (Pichler and Tilch (2004)). Drug-induced immune hemolytic anemia (DIIHA) due to an autoimmune mechanism may occur in cases of drug-induced fever without skin symptoms and has been reported for antimalarial agents such as artesunate (Raffray et al., 2014; Camprubí et al., 2019). Although a direct antiglobulin test was not performed in this case, severe anemia and elevated bilirubin were not observed around the time when fever has recurred, and the patient was considered unlikely to have had DIIHA.

Although in vitro studies such as DLST might be helpful, in many cases, fever is relieved by discontinuation of the causative drug and is a clue to drug fever diagnosis. The fever is usually relieved within 72–96 h after discontinuing the causative drug (MacDonald and Sexton, 2021). The most effective way to make a definitive diagnosis of drug fever is a challenge test, but this was not possible in our case from an ethical standpoint. In our patient, mild eosinophilia was accompanied by an increase in leukocytosis and a slightly delayed increase in CRP, the favipiravir-induced DLST was positive, and fever was relieved about 72 h after the discontinuation of favipiravir. Based on these factors, a diagnosis of drug fever with favipiravir was definitively established.

Favipiravir treatment for from 10 days to 2 weeks is currently suggested for the treatment of COVID-19. However, as in our case, drug fever after 10 days of favipiravir was described in a case report by Takoi and his colleagues (Takoi et al., 2020). Also, Kurita et al. reported that the favipiravir-induced drug fever occurred about a week after administration (Kurita et al., 2020).

We measured the blood levels of favipiravir, administered to treat COVID-19, in serum from our patient (Figure 2). The favipiravir blood concentration was maintained at about 60–70 mg/L up to day 13 of treatment with favipiravir, decreasing to 0.15 mg/L on day 15 after discontinuation of favipiravir. After discontinuation of oral favipiravir, it was promptly cleared from the

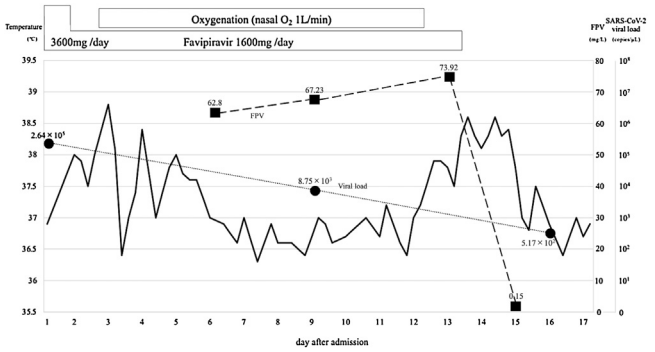

Figure 2. The trends over time in favipiravir blood level, body temperature and viral load.

blood in association with rapid resolution of fever. The drug fever in this case was thought to be an allergic reaction and not dose-dependent, and no previous data has been found on the correlation between favipiravir blood levels and its side effects. However, in this case, favipiravir was taken for more than 1 week even after the clinical findings improved and the viral load decreased, which may lead to the onset of drug fever, suggesting that a shorter dose of about 1 week may have been sufficient. Future studies are needed to elucidate the relationship.

ICMJE statement

All authors meet the ICME authorship criteria.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Ethical approval

This study was performed in accordance with the Helsinki Declaration and approved by the Ethical Review Board of the University of Toyama (approval Nos.: R2019167 and R2020146).

Author contributions

Y. Murai, H. Kawasuji, and Y. Yamamoto wrote the manuscript and took care of the patient. Y. Takegoshi, M. Kaneda, K. Kimoto, A. Ueno, Y. Miyajima, K. Kawago, Y. Fukui, and I. Sakamaki took care of the patient. C. Ogami and Y. Tsuji measured blood concentration. Y. Morinaga measured the viral load. All authors have read and approved the final report.

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