Successful treatment of COVID-19 with colchicine in a kidney transplant recipient

Satoko Nozato, MD, PhD[a]*; Akane Ito, MD[a]; Ken Terashima, MD[b]; Yoichi Nozato, MD, PhD[c]; Yuki Yoshii, MD[b]; Kaori Seki, MD[a]; Ryota Yoshimoto, MD[a]; Atsuyuki Morishima, MD, PhD[b]; Katsuhiko Sakaguchi, MD, PhD[b]; and Masayasu Kitano, MD, PhD[a]

[a]*Division of Immunology and Rheumatology, Sumitomo Hospital, Osaka, Japan.*

[b]*Kidney Center, Sumitomo Hospital, Osaka, Japan.*

[c]*Department of General Internal Medicine, Osaka University Hospital, Osaka, Japan.*

*** Corresponding author**:

Satoko Nozato, MD, PhD

Division of Immunology and Rheumatology, Sumitomo Hospital, Osaka, Japan

5-3-20 Nakanosima, Kita-ku, Osaka, 530-0005, Japan

Tel +81-6-6443-1261, Fax +81-6-6444-3975,

E-mail: satoko.nozato@geriat.med.osaka-u.ac.jp

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Learning point for clinicians

Colchicine has anti-inflammatory properties and rarely weakens the immune system.

In the context of coronavirus disease 2019 (COVID-19), hyperinflammation may last in the subacute phase in rare cases of immunosuppressed patients, even after negative reverse transcription-polymerase chain reaction (RT-PCR) results are obtained.

Colchicine can be an optional therapy for hyperinflammation after viral clearance.

Case Report

A 36-year-old man was diagnosed with COVID-19 because of fever, atypical pneumonia, and a positive RT-PCR result (day 1). He had undergone immunosuppressive therapy, including prednisolone (5 mg/day), tacrolimus (6 mg/day), mycophenolate mofetil (MMF; 1000 mg/day), and everolimus (3 mg/day), since having kidney transplantation due to immunoglobulin-A nephropathy at age 34. His COVID-19-related pneumonia was treated with methylprednisolone (40 mg/day). RT-PCR results were negative for COVID-19 after day 23, despite persistent fever of 38–40°C and C-reactive protein (CRP) levels >100 mg/L, followed by erythema of the right thigh and poly-arthralgia. Computed tomography revealed panniculitis and mild pericardial effusion. On presentation to a rheumatologist, his vital signs were stable, except for a temperature of 38.8°C, and his general appearance was good. His immunosuppressive therapy then included prednisolone (15 mg/day), tacrolimus (6 mg/day), MMF (500 mg/day), and everolimus (1.5 mg/day). Laboratory examination revealed the following: white blood cell count, 12300/mm^3; haemoglobin level, 7.9 g/dL; creatinine level, 2.1 mg/dL; CRP level, 117 mg/L;

antinuclear antibody titer, 1:40; C3 level, 145 mg/dL; C4 level, 30 mg/dL; and serum interleukin (IL)-6 level, 149 pg/ml. Blood, sputum, and urine cultures were negative. Gallium-67 scintigraphy showed a normal distribution. Erythema, poly-arthralgia, and pericardial fluid suggested an abnormality in innate immunity. Increasing the dosage of corticosteroids was considered, but there were concerns about new infections. Therefore, we chose colchicine because of its safety against infectious diseases, and its effect on pericarditis.[1] Colchicine (0.5 mg/day) was initiated on day 51 (Figure 1). He became afebrile and asymptomatic within two days, with decreased CRP (<0.3 mg/L) and IL-6 (0.8 pg/mL) levels. Colchicine therapy was completed in four weeks, and fever has not recurred.

Discussion

There have been many reports on colchicine's effectiveness[2] or ineffectiveness[3] in the acute phase of COVID-19. However, to the best of our knowledge, this is the first report that shows the usefulness of colchicine in treating persistent hyperinflammation in the subacute phase after negative conversion of viral RNA in COVID-19.

Immunocompetent cells play two major roles in COVID-19 infection: hyperinflammation and virus excretion.[4] Hyperinflammation includes hyper-activation of inflammasomes, which leads to IL-1β activation in innate immunity. Pathogen-associated molecular patterns activate NF-κB transcription and inflammasomes via toll-like receptors in macrophages, resulting in a robust and rapid innate immune response, including IL-1β and IL-6. We initially assumed that delayed virus excretion caused febrile illness since immunosuppressant drugs suppressed significant immune components for viral clearance, such as interferon-γ and cytotoxic T lymphocytes. However, in the context of negative RT-PCR results and elevated IL-6 levels, it was likely that IL-6, and not

viral cytotoxicity, induced a hyperinflammatory response.[5] Moreover, as IL-1β is capable of promoting IL-6 expression,[6] IL-1β from circulating monocytes may induce hyperinflammation.

Tocilizumab, an anti-IL-6 receptor antibody, is an alternative for suppressing hyperinflammation. However, we were concerned that leukopenia, a common complication of tocilizumab, may increase infections such as cytomegalovirus infection and fungal infection in compromised hosts. On the other hand, colchicine can be administered without any notable long-term side effects of infectious diseases for autoinflammatory syndromes.[1] Moreover, colchicine has anti-inflammatory effects by inhibiting inflammasome activation in innate immunity and blocking IL-1β expression.[2]

Colchicine, selected as a safer drug, showed a remarkable impact as a result. It is noteworthy that the patient's symptoms mimicked autoinflammatory syndromes.

Conclusion

Hyperinflammation due to innate immunity dysregulation may occur in the subacute phase after negative conversion of viral RNA in immunosuppressed patients with COVID-19. The effectiveness of colchicine suggests that the inflammasome is key to the pathophysiology of hyperinflammation after viral clearance. However, further investigation is required on the effectiveness of colchicine treatment during subacute hyperinflammation in COVID-19.

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Figure legend

Figure 1

Clinical course of the patient.

The patient had a fever for more than four weeks after negative COVID-19 RT-PCR results. He became afebrile and asymptomatic within two days after starting colchicine, with the normalization of CRP and serum IL-6 levels.

COVID-19, coronavirus disease 2019; RT-PCR, reverse transcription-polymerase chain reaction; IL-6, interleukin-6; PSL, prednisolone; Tac, tacrolimus; MMF, mycophenolate mofetil; EVL, everolimus.

Abbreviations definition list

COVID-19 - coronavirus disease 2019

CRP - C-reactive protein

EVL - everolimus

IL - interleukin

IL-6 - interleukin-6

MMF - mycophenolate mofetil

PSL - prednisolone

RT-PCR - reverse transcription-polymerase chain reaction

Tac - tacrolimus

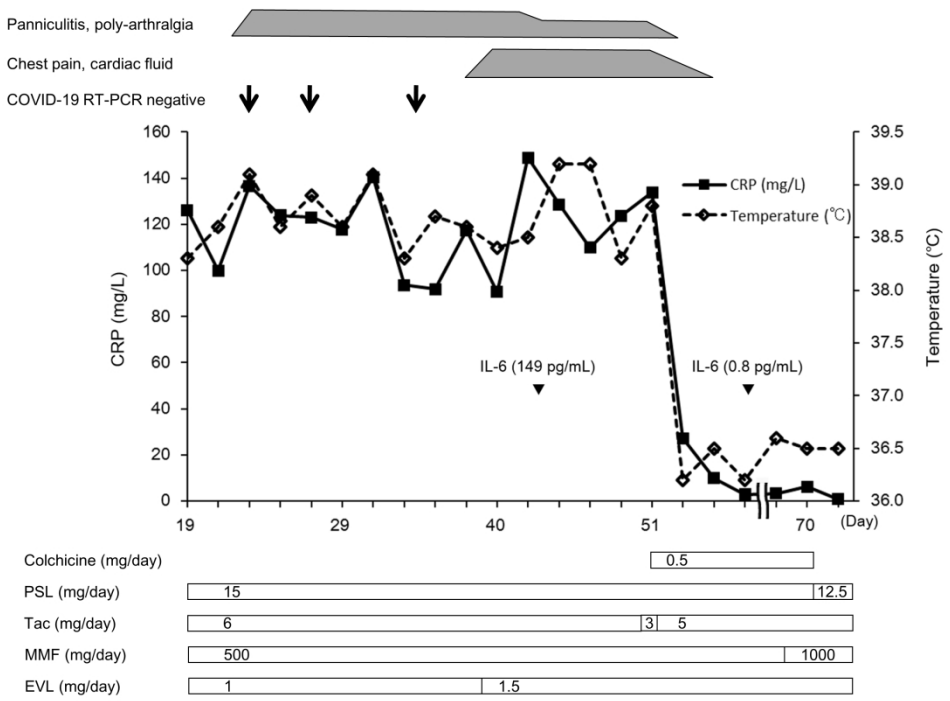

Figure 1 Clinical course of the patient. The patient had a fever for more than four weeks after negative COVID-19 RT-PCR results. He became afebrile and asymptomatic within two days after starting colchicine, with the normalization of CRP and serum IL-6 levels.%"COVID-19, coronavirus disease 2019; RT-PCR, reverse transcription-polymerase chain reaction; IL-6, interleukin-6; PSL, prednisolone; Tac, tacrolimus; MMF, mycophenolate mofetil; EVL, everolimus.

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