Clinical case

Reactive arthritis after COVID-19 infection

Keisuke Ono,1 Mitsumasa Kishimoto,1 Teppei Shimasaki,2 Hiroko Uchida,1 Daisuke Kurai,2 Gautam A Deshpande,3 Yoshinori Komagata,1 Shinya Kaname1

ABSTRACT
Reactive arthritis (ReA) is typically preceded by sexually transmitted disease or gastrointestinal infection. An association has also been reported with bacterial and viral respiratory infections. Herein, we report the first case of ReA after the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. This male patient is in his 50s who was admitted with COVID-19 pneumonia. On the second day of admission, SARS-CoV-2 PCR was positive from nasopharyngeal swab specimen. Despite starting standard dose of favipiravir, his respiratory condition deteriorated during hospitalisation. On the fourth hospital day, he developed acute respiratory distress syndrome and was intubated. On day 11, he was successfully extubated, subsequently completing a 14-day course of favipiravir. On day 21, 1 day after starting physical therapy, he developed acute bilateral arthritis in his ankles, with mild enthesitis in his right Achilles tendon, without rash, conjunctivitis, or preceding diarrhoea or urethritis. Arthrocentesis of his left ankle revealed mild inflammatory fluid without monosodium urate or calcium pyrophosphate crystals. Culture of synovial fluid was negative. Plain X-rays of his ankles and feet showed no erosive changes or enthesophytes. Tests for syphilis, HIV, anti-streptolysin O (ASO), Mycoplasma, Chlamydia pneumoniae, antinuclear antibody, rheumatoid factor, anticyclic citrullinated peptide antibody and Human Leukocyte Antigen-B27 (HLA-B27) were negative. Gonococcal and Chlamydia trachomatis urine PCR were also negative. He was diagnosed with ReA. Nonsteroidal Anti-Inflammatory Drug (NSAID)s and intra-articular corticosteroid injection resulted in moderate improvement.

INTRODUCTION
Reactive arthritis (ReA) is a known entity, typically causing asymmetric monoarthritis or oligoarthritis involving lower limbs (ankles and knees), and usually occurring 1–3 weeks after sexually transmitted or gastrointestinal infection.1 Although less described in the literature, respiratory bacterial infections such as Chlamydia psittaci, Chlamydia pneumoniae, Staphylococcus aureus and Streptococcus pneumoniae or viral infections have been associated with some cases of ReA. Herein, we report the first case of ReA after SARS-CoV-2 infection.

CASE REPORT
This male patient is in his 50s who was admitted for COVID-19 pneumonia. He had a medical history of steatohepatitis. He was in his usual state of health until 5 days prior to admission when he developed fever with chills and severe fatigue. He was referred to our hospital from a neighbouring clinic for unremarkable symptoms. At admission, he was mildly hypoxic (SpO2 of 95% in room air) and laboratory tests showed white blood cell (WBC) of 3.6×10^9/μL, platelet of 12.3×10^4/μL, serum creatinine of 1.85 mg/dL, lactic dehydrogenase (LDH) of 39 8IU/L and C-reactive protein (CRP) of 8.31 mg/dL (table 1). Chest CT scan revealed bilateral ground-glass opacities, and he was admitted to the high care unit for suspected COVID-19 pneumonia. On the second day of admission, SARS-CoV-2 PCR was positive from nasopharyngeal swab specimen. Despite starting standard dose of favipiravir, his respiratory condition deteriorated during hospitalisation. On the fourth hospital day, he developed acute respiratory distress syndrome and was intubated, receiving supportive care with empiric cefepime and vancomycin. After confirming negative sputum and blood cultures, both antibiotics were stopped after 5 and 2 days of therapy, respectively. On day 11, he was successfully extubated and completed a

What is already known about this subject?
► ReA typically manifests asymmetric monoarthritis or oligoarthritis involving lower limbs (ankles and knees), usually occurs 1–3 weeks after a sexually transmitted disease or gastrointestinal infection.
► Respiratory bacteria and virus might cause ‘ReA’.

What does this study add?
► SARS-CoV-2 infection may cause ‘ReA’.

How might this impact on clinical practice?
► In patients with acute arthritis after COVID-19 infections, ‘ReA’ should be considered.


K0, MK and TS contributed equally to this clinical case

Received 2 June 2020
Revised 10 July 2020
Accepted 18 July 2020

© Author(s) (or their employer(s)) 2020. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

1Department of Nephrology and Rheumatology, Kyorin University School of Medicine, Shinkawa, Mitaka-shi, Tokyo, Japan
2Department of Infectious Disease, Kyorin University School of Medicine, Shinkawa, Mitaka-shi, Tokyo, Japan
3Department of Internal Medicine, University of Hawaii at Manoa John A Burns School of Medicine, Honolulu, Hawaii, USA

Correspondence to
Mitsumasa Kishimoto; kishimotom@gmail.com
14-day course of favipiravir with clinical resolution of pneumonia. On day 21, 1 day after starting physical therapy, he developed acute bilateral arthritis in his ankles, with mild enthesitis in his right Achilles tendon. He had no rash, conjunctivitis, or preceding diarrhoea or urethritis. Arthrocentesis of his left ankle revealed mild inflammatory fluid without monosodium urate (MSU) and calcium pyrophosphate crystals. Culture of synovial fluid was also negative. Plain X-rays of his ankles and feet showed no erosive changes or enthesophytes. Tests for syphilis, HIV, ASO, Mycoplasma, Chlamydia pneumoniae, antinuclear antibody, rheumatoid factor, anticyclic citrullinated peptide antibody and HLA-B27 were negative (table 2). Gonococcal and Chlamydia trachomatis urine PCR were also negative. He was diagnosed with ‘ReA’; NSAIDs and intra-articular corticosteroid injection resulted in moderate improvement.

**DISCUSSION**

SARS-CoV-2 is now known to cause a host of extrapulmonary complications, including cardiovascular, neurologic and dermatologic sequelae, many occurring or lasting for weeks after infection. We report the first case of ‘ReA’ after SARS-CoV-2 infection.

<table>
<thead>
<tr>
<th>Laboratory findings of clinical course</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>On admission (day 1)</strong></td>
</tr>
<tr>
<td>WBC (cells/mm³, 3300–8600)</td>
</tr>
<tr>
<td>Neutrophil (%)</td>
</tr>
<tr>
<td>Lymphocyte (%)</td>
</tr>
<tr>
<td>Eosinophil (%)</td>
</tr>
<tr>
<td>Monocyte (%)</td>
</tr>
<tr>
<td>Basophil (%)</td>
</tr>
<tr>
<td>Atypical lymphocyte (%)</td>
</tr>
<tr>
<td>Haemoglobin (g/L, 137–168)</td>
</tr>
<tr>
<td>Platelet (×10⁶/μL, 15.8–34.8)</td>
</tr>
<tr>
<td>BUN (mg/dL, 8.0–20.0)</td>
</tr>
<tr>
<td>Creatinine (mg/dL, 0.65–1.07)</td>
</tr>
<tr>
<td>Uric acid (mg/dL, 3.7–7.8)</td>
</tr>
<tr>
<td>AST (IU/L, 13–30)</td>
</tr>
<tr>
<td>CK (IU/L, 59–248)</td>
</tr>
<tr>
<td>LDH (IU/L, 124–222)</td>
</tr>
<tr>
<td>Bilirubin (mg/dL, 0.4–1.5)</td>
</tr>
<tr>
<td>CRP (mg/dL, 0.00–0.14)</td>
</tr>
<tr>
<td>D-dimer (μg/mL, 0.0–1.0)</td>
</tr>
<tr>
<td>Procalcitonin (ng/mL, 0.0–0.50)</td>
</tr>
</tbody>
</table>

WBC, white blood cell; BUN, blood urea nitrogen; AST, aspartate transaminase; CK, creatine kinase; LDH, lactic dehydrogenase.

No diagnostic or classification criteria have been established for ReA, but the American College of Rheumatology has issued general guidelines, and in 1999, the 4th International Workshop on ReA discussed the term ‘reactive arthritis’, proposing its use only for a clinical picture and microbes associated with HLA-B27 and spondyloarthritis. Consequently, the definition of ReA is now based on a diagnostic criterion (table 3) that largely focuses on enteral or urethral infections. However, we previously reported a case of clinical ReA after HIV infection; a syndrome consistent with ReA has also been reported with dengue and chikungunya virus, parvovirus B19, rubella and measles vaccines. In our case, the arthritis occurred precisely 3 weeks after the infectious episode; without a competing source of identifiable extra-articular infection, and synovial fluid cultures negative for bacteria, we are strongly led to a diagnosis of clinical ReA.

ReA tends to occur most often in men between ages 20 and 50. A 30–50% of patients with ReA carry HLA-B27. Although patients without HLA-B27 can develop ReA, as is in our case, some degree of genetic susceptibility is considered necessary, since ReA occurs in only 7–15% of infected population-level subjects. The association of
A limitation of our study is that viral arthritis is also a known entity and we are unable to completely exclude an acute viral arthritis, though this typically occurs during the acute fever episode,11 and the pattern described here was notably different. Additionally, bacterial coinfections are reported in severe COVID-19 patients12 and ReA due to an occult bacterial respiratory coinfection is possible. However, sputum and blood cultures prior to initiation of empirical antibiotics failed to identify a competing bacterial cause, and the clinical course was not consistent with occult infection. Finally, our patient developed mild hyperuricemia, a known side effect of favipiravir,13 and raising the possibility of a crystal arthropathy as a cause of symptoms. Careful synovial fluid analysis did not identify MSU crystals, which ruled out gouty arthritis.

To conclude, we report the first case of ‘ReA’ after SARS-CoV-2 infection. Our findings offer an opportunity to improve both early diagnosis and treatment of ‘ReA’ during the COVID-19 pandemic.

A ‘definite’ diagnosis of ReA is based on the fulfilment of both major criteria and a relevant minor criterion, while a ‘probable’ diagnosis is characterised by both major criteria but no relevant minor criterion or one major criterion and one or more of the minor criteria. The identification of the trigger infection is also required.

HLA-B27 and ReA is further illustrated by the fact that the prevalence of disease in HLA-B27-positive individuals is five times greater than in the general population. In HLA-B27-positive relatives of patients with ReA, the prevalence is an additional 10 times greater.9 Moreover, HLA-B27 positivity may be a poor prognostic factor, as a previous study has shown that the presence of HLA-B27 in ReA has been linked to more severe disease, higher frequencies of sacroiliitis and extra-articular manifestations, and an increased likelihood of persistent arthropathy.10

Acknowledgements The authors thank the COVID-19 team at Kyorin University School of Medicine.

Contributors All authors contributed drafting of this manuscript. KO, MK and TS contributed equally to this clinical case. All authors contributed drafting of this manuscript. KO, MK and TS contributed equally to this clinical case.

Ethics approval We have obtained consent from our patient.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the clinical case are included in the article.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iD Keisuke Ono http://orcid.org/0000-0002-2651-1509

REFERENCES

HLA-B27 and ReA is further illustrated by the fact that the prevalence of disease in HLA-B27-positive individuals is five times greater than in the general population. In HLA-B27-positive relatives of patients with ReA, the prevalence is an additional 10 times greater.9 Moreover, HLA-B27 positivity may be a poor prognostic factor, as a previous study has shown that the presence of HLA-B27 in ReA has been linked to more severe disease, higher frequencies of sacroiliitis and extra-articular manifestations, and an increased likelihood of persistent arthropathy.10

A limitation of our study is that viral arthritis is also a known entity and we are unable to completely exclude an acute viral arthritis, though this typically occurs during the acute fever episode,11 and the pattern described here was notably different. Additionally, bacterial coinfections are reported in severe COVID-19 patients12 and ReA due to an occult bacterial respiratory coinfection is possible. However, sputum and blood cultures prior to initiation of empirical antibiotics failed to identify a competing bacterial cause, and the clinical course was not consistent with occult infection. Finally, our patient developed mild hyperuricemia, a known side effect of favipiravir,13 and raising the possibility of a crystal arthropathy as a cause of symptoms. Careful synovial fluid analysis did not identify MSU crystals, which ruled out gouty arthritis.

To conclude, we report the first case of ‘ReA’ after SARS-CoV-2 infection. Our findings offer an opportunity to improve both early diagnosis and treatment of ‘ReA’ during the COVID-19 pandemic.

A ‘definite’ diagnosis of ReA is based on the fulfilment of both major criteria and a relevant minor criterion, while a ‘probable’ diagnosis is characterised by both major criteria but no relevant minor criterion or one major criterion and one or more of the minor criteria. The identification of the trigger infection is also required.