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Severe Acute Respiratory Syndrome Coronavirus 2 Omicron Variant Kinetics in Natural Infection: A Case Study

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ABSTRACT

Background Omicron has become the mainstream epidemic variant of severe acute respiratory syndrome coronavirus 2 worldwide. One reason for the high infectivity of this variant is its ability to multiply rapidly in the human body. It has been speculated that, in general, the short period required for virus multiplication affects the incubation period and timing of viral shedding that begins during the incubation period. However, it is unclear whether these effects can be related to the Omicron variant. Similar to a recent human challenge study, in this study, patients with known timing of Omicron infection were followed up in a hospital before the onset of the disease.

Methods In two patients, the viral shedding was investigated and analysed along with symptoms before and after the disease onset.

Results The incubation period for Omicron was 30-36 h; this was shorter than the average incubation period of the alpha variant in the human challenge study and that reported in a systematic review and meta-analysis (3.5 days). Viral shedding at the nasal site began 19-22 h after infection, approximately 10 h before symptom onset.

Conclusion The results of this study demonstrated that in some instances with Omicron (BA.5), the time to viral shedding and the time to disease onset were considerably shorter after infection than those previously reported for Omicron and Alpha variants. We showed the importance of early detection of the viral antigen after viral exposure and early isolation initiation to prevent infection spread.

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected approximately 762 million people worldwide since the coronavirus disease (COVID-19) pandemic began and was associated with more than 6 M deaths worldwide by April 2023.[1] Since the emergence of the virus in Wuhan, China, in December 2019, various new variants have been identified. The high infectivity and transmissibility patterns of the virus have led to an increased vigilance for variants of concern (VOCs).[2] Omicron (B.1.1.529), a VOC that emerged in 2020, has become predominant within its short history, spreading worldwide at an unprecedented rate and generating new cases of infection. Several likely reasons have been suggested for the high infectivity of Omicron, one of which is its numerous mutations in high-infectivity regions.[3,4] Furthermore, mutations and deletions in its spike protein have led to a critical situation wherein specific therapies for patients infected with up to the delta variant level are not optimal for Omicron-infected patients.[5] One of the reasons for the rapid spread of Omicron is its increased adaptation to humans and rapid proliferation in the human body.[6,7] It has been suggested that increased viral replication may lead to earlier viral shedding and a shorter incubation period.[8] The mean incubation period of Omicron is 3.5-3.6 days[9,10], indicating a gradual reduction in the incubation period compared with those of the past epidemic variants. However, the timing of infection in infected individuals, the subject of these analyses, is only an estimate. Regarding the timing of viral shedding during incubation, a recent human challenge study on the alpha variant confirmed that viral shedding begins within two days after infection.[11] However, data for Omicron still need to be included. Due, in part, to the difficulty of obtaining specimens from infected patients before the onset of COVID-19 and to the difficulty of carrying out human challenge studies, the exact incubation period and the onset of viral excretion during the incubation period for the Omicron variant is still being.

As in the human challenge study, we had two patients in whom the time of infection with Omicron was precise, and the nasal viral load and clinical course were analysed over time immediately after infection. Although this is a case report, we compare the viral dynamics of Omicron during the incubation period with those reported previously and discuss the usefulness of viral antigen testing during the incubation period and the need to prevent the spread of infection.

CASE REPORT

Two patients who may have been infected with SARS-CoV-2 in December 2022 and January 2023 were included in this study. The patients were admitted to Jichi Children's Medical Center Tochigi and were asymptomatic immediately after the exposure to SARS-CoV-2. On admission, the film array of respiratory specimens, which was subjected to extensive screening tests, was negative for the virus and bacterial antigens. SARS-CoV-2-specific IgM and nucleocapsid IgG antibody tests using chemiluminescent enzyme immunoassay also tested negative. After admission, vital signs were measured multiple times daily; anterior nasal and nasopharyngeal nasal swab samples for viral load measurement and blood samples for antibody titer measurement were collected continuously.

Viral RNA was extracted from nasal specimens using QIAamp Viral RNA Mini Kit (Qiagen, Hilden, Germany), and real-time polymerase chain reaction (RT-PCR) was performed using Reliance One-Step Multiplex Supermix (Bio-Rad Laboratories, California, USA) according to the National Institute of Infectious Disease protocol.[12] This study was approved by the Jichi Medical University Hospital Research Ethics Review Committee (approval number 21-100), and written informed consent was obtained from the participants. Written consent was obtained from a surrogate parent or guardian for the participant who was <18 years old.

Case 1 was an 18-year-old female patient with no history of COVID-19 and SARS-CoV-2 vaccination. She was exposed to a COVID-19 patient for approximately 2 h during lunch at home and was admitted to our hospital 5 h after the last contact (LC). On admission, SARS-CoV-2 RT-PCR results for the nasopharyngeal and anterior nasal samples were negative, and blood tests and chest radiographs showed no abnormal findings. SARS-CoV-2 RT-PCR result was negative until 12 h after the LC. The nasopharyngeal site sample tested positive for the SARS-CoV-2 antigen (lineage BA.5.2.1) for the first time 19 h after the LC, with a Cycle threshold (Ct) value of 36.9. Subsequently, 36 h after the LC, the patient developed a dry cough and sore throat, and 42 h after the LC, the patient developed a fever of 38.6 °C. The highest Ct values were 19.5 at 47 h after the LC for the anterior nasal sample and 17.3 at 64 h after the LC for the nasopharyngeal sample. We explained

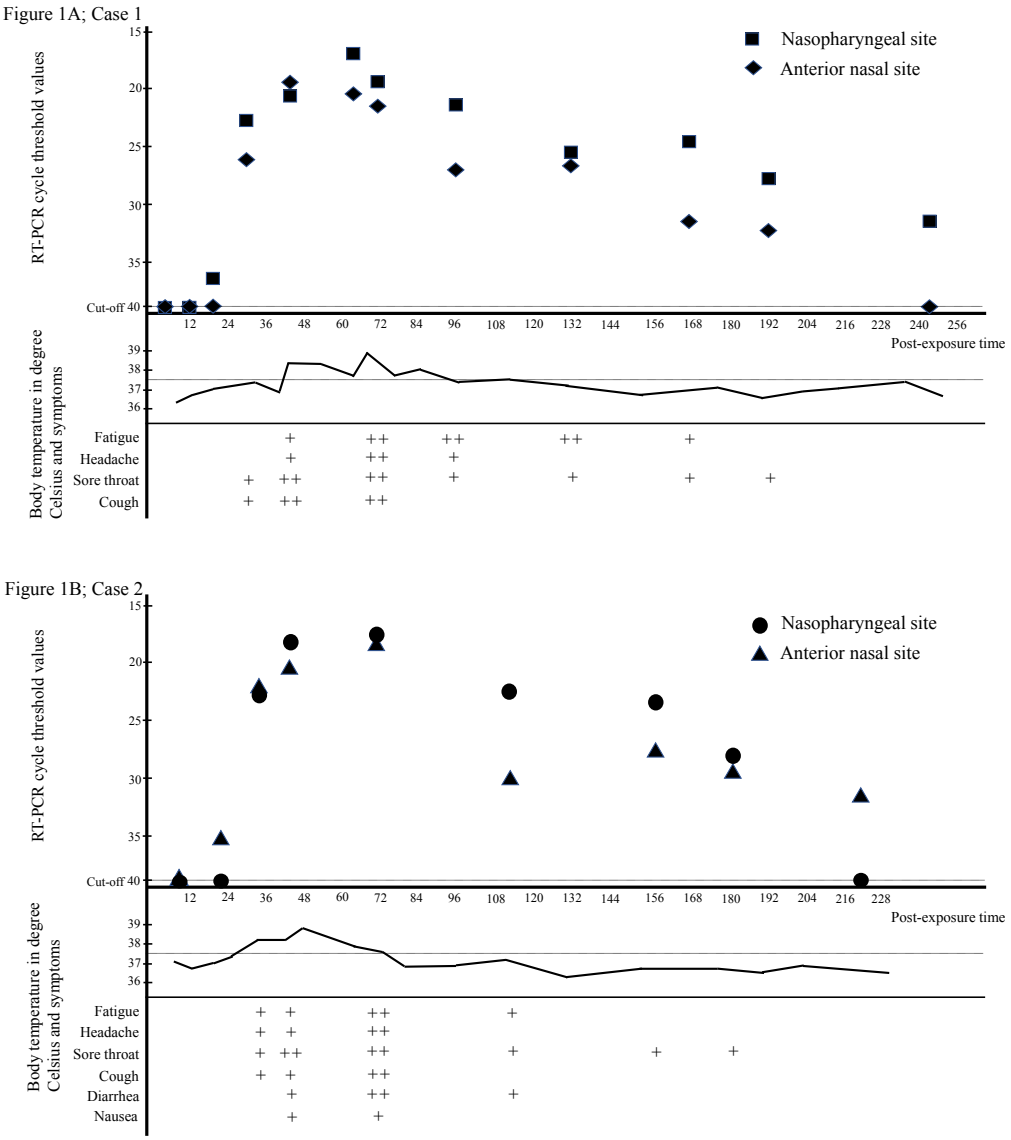

Figure 1. Viral dynamics and symptoms after Omicron variant infection in the two cases. Nasal specimens were collected from the anterior nasal and nasopharyngeal sites simultaneously. The cut-off value for RT-PCR was set at 40. Clinical symptoms were assessed at the time of specimen collection from the nasal cavity. One and two plus indicated mild and severe symptoms, respectively. No description was provided for asymptomatic patients. (A) Ct values for the anterior nasal site were shown using the diamond symbol, whereas those for the nasopharyngeal site are indicated as squares. (B) Ct value for the anterior nasal site was established as a triangle, whereas that for the nasopharyngeal site was established as a circle.

antivirals and other COVID-19 medications to the family and the patient; however, they expressed their reluctance to use any therapeutic agents other than antipyretics. Therefore, we used acetaminophen thrice a day as the maximum frequency of use when the patient complained of general malaise and headache at a body temperature ≥37.5 °C. Ninety-six hours after the LC, the fever resolved, and the symptoms rapidly improved. Subsequently, general malaise and sore throat persisted for >70 h. Viral shedding persisted for more than 240 h and 150 h after the LC and post-febrile, respectively *(Figure 1A).* Serum IgM tested positive 166 h after the LC, and serum IgG tested positive 192 h after the LC.

Case 2 was a 13-year-old female patient with no history of COVID-19 and SARS-CoV-2 vaccination. She was exposed to a COVID-19 patient during a 3-hour dinner party at home. She was admitted to the hospital 9 h after the LC. Upon admission, RT-PCR results for nasal specimens taken from anterior nasal and nasopharyngeal sites were negative, and blood tests and chest radiographs showed no abnormal findings. Twenty-two hours after the LC, the patient was asymptomatic; however, RT-PCR was positive for the SARS-CoV-2 antigen (lineage BA.5.2) for the anterior nasal specimen. The Ct value at this time was

35.0. We explained to the family and the patient the available COVID-19 medications of choice; however, they did not wish to use any other therapeutic agents except antipyretics. After that, the Ct values of both nasal samples decreased over time. The lowest Ct values were recorded at 71 h after the LC, 18.7 for the anterior nasal sample and 18.1 for the nasopharyngeal sample. Thirty-four hours after the LC, general malaise, fever of 38°C, dry cough, and sore throat developed. Seventy-one and 112 h after the LC, the fever had resolved and improved, respectively. Sore throat persisted for approximately 110 h after the resolution of the fever. Viral shedding continued for > 200 hours after the LC and 140 hours after the fever had broken *(Figure 1B)*. Furthermore, serum IgM tested positive 217 h after the LC; however, serum IgG did not test positive.

No radiographic or blood test abnormalities were found during hospitalisation for either patient.

DISCUSSION

Both the time to viral shedding and the incubation period after infection with the Omicron was short for both cases. The case results from the two cases highlight the importance of testing for viral antigens during the incubation period and initiating surgical masks and isolation as early as possible after viral exposure to prevent the spread of infection in home and group settings.

In our patients, viral shedding based on the nasal sample testing began during the 19-22 h incubation period after the LC. Compared with the alpha variant[11] for which viral shedding occurs 40 h after infection, in this study the Omicron variant shedding occurred earlier. This suggests that testing early after viral exposure, i.e., before the onset of disease, may be helpful; however, it should also be considered that at high Ct values, i.e., low viral loads, the possibility of false-negative result occurs with antigen-detection rapid diagnostic tests that do not amplify viral genes, although RT-PCR can provide an accurate diagnosis. The subsequent viral load trends were similar to those previously reported[13], with the nasopharyngeal site illustrating more viral shedding than the anterior nasal site; furthermore, viral shedding was observed for more than ten days after onset. A systematic review and meta-analysis reported the mean incubation period to be 3.5 days.[9] Although the reason is not apparent, it should be noted that some patients, like our patients, may be infected with the same variant of Omicron but with a much shorter incubation period of 30–36 h. A study by Ogata *et al*.[14], published several months prior, involving patients infected with Omicron, reported that the incubation period of Omicron had shortened to an average of about 2.6 days.

CONCLUSIONS

By inference, Omicron, which has been spreading since 2021, may have undergone genetic mutations[15] due to viral multiplication, resulting in increased efficiency of viral multiplication in the human body, which may be one of the reasons for early viral shedding after infection and shortened incubation period. Our results indicate that post-exposure measures must be taken sooner than before to prevent the spread of Omicron.

Conflict of Interest

The authors declare no conflicts of interest.

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Author Contributions

Conceptualization, D.T., H.Y.; materials, D.T., H.Y., K.K.; Patient care and specimen collection, D.T., H.Y., K.K.; Data collection, D.T.; Analysis, D.T.; Literature review, H.T., H.O.; Writing-original draft preparation, D.T., H.Y., K.K.; Critical review and editing, D.T., H.Y., K.K. H.T., H.O; Supervision, H.T., H.O.; Funding acquisition, D.T.

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