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Case Report

Vaginal delivery after improvement in COVID-19 by monoclonal antibody treatment: A case report and literature review

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A R T I C L E   I N F O

Keywords:
COVID-19
Lactation
Monoclonal antibody treatment
Pregnancy
Vaginal delivery

A B S T R A C T

As the COVID-19 pandemic persists, pregnant women have been increasingly affected worldwide. Women during the last trimester of pregnancy are susceptible to severe COVID-19, and there are many challenges towards its treatment. Monoclonal antibody treatment (MAT) is approved for COVID-19 patients to reduce disease severity. However, there are few reports on the MAT in perinatal women. Herein, we report a 39-year-old pregnant female (36 weeks and 6 days of gestation) with improvement in COVID-19 pneumonia after treatment with casirivimab/imdevimab, resulting in successful vaginal delivery (a 2.868 kg male newborn), along with a literature review. Early diagnosis and treatment of pregnant women with COVID-19 are important. Infectious diseases doctors and/or obstetricians should be aware of the MAT option administered to perinatal COVID-19 women to reduce disease severity.

1. Introduction

COVID-19 is an infectious disease caused by SARS-CoV-2 and is prevalent worldwide. The infection rate and risk of hospitalization for COVID-19 have been reported to increase during pregnancy, and there is a strong concern about the severity of the disease among this population [1–3]. Pregnant women with COVID-19 have a 3 to 4-folds high risk of being severely ill or hospitalized compared to non-pregnant COVID-19 patients [1, 4, 5]. Additionally, the risk of death was reported to be about 13-times higher in gravid patients [1]. Drugs available during both pregnancy and lactation, as well as monoclonal antibody treatment (MAT), may be beneficial in obstetric/perinatal situations. MATs are useful particularly for managing patients with rheumatoid arthritis and inflammatory bowel diseases; tumor necrosis factor-α (TNF-α) inhibitors are considered safe to administer based on epidemiological studies and clinical experiences [6–9]. Casirivimab and imdevimab (C&I, Ronapreve™) combination treatment was approved to attenuate the severe progression of COVID-19 under emergency use permission from the Ministry of Health, Labour and Welfare during the Japanese 5th epidemic in 2021. C&I is a co-package of two neutralizing immunoglobulin gamma 1 human monoclonal antibodies against the Spike protein, especially the receptor-binding domain. However, there are few reports regarding the MAT of perinatal COVID-19 women. We herein report a 39-year-old pregnant woman (36 weeks and 6 days of gestational age) with improvement in COVID-19 pneumonia after treatment with C&I, resulting in successful vaginal delivery, along with a literature review.

Abbreviations: ADA, adalimumab; C&I, casirivimab and imdevimab; ETN, etanercept; IFX, infliximab; IL, interleukin; LAMP, loop-mediated isothermal amplification; MAT, monoclonal antibody treatment; RT-PCR, reverse transcription-polymerase chain reaction; SpO2, percutaneous saturation of oxygen; TARC, thymus and activation-regulated chemokine; TNF-α, tumor necrosis factor-α.

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https://doi.org/10.1016/j.jiac.2022.02.023
Received 18 January 2022; Received in revised form 21 February 2022; Accepted 24 February 2022
2. Case report

Japanese medical care providers were facing the 5th COVID-19 epidemic (from the end of June through the end of September 2021). On the August 20th, the maximum number of newly SARS-CoV-2-infected individuals reached 25,851/day. The Minami-Nagano Medical Center was requested to accept the maternal transport of a 39-year-old pregnant female at 36 weeks and 6 days of gestation from a local hospital, who had already revealed positive results for the SARS-CoV-2 antigen test. The patient had a history of two uncomplicated vaginal deliveries and two spontaneous abortions without underlying diseases. She had not received a vaccination(s) against COVID-19. Her pregnancy was uneventful. Fever (more than 37 °C) as well as cough, malaise, and anorexia, occurred on August 25th, 2021. The patient was immediately admitted to our hospital six days later. Physical findings on admission showed a body temperature of 38.1 °C, blood pressure of 98/60 mmHg, pulse rate of 60 beats/min, percutaneous saturation of oxygen (SpO₂) 95% (under room air), and respiratory rate 18/min. Although she had been positive for the antigen test, a local public health center requested us to detect the genes. Using nasopharyngeal specimens on admission, a comprehensive respiratory pathogen detection system (FilmArray Respiratory Panel 2.1™) to amplify Spike/Matrix genes of SARS-CoV-2 was conducted in the hospital. A real-time reverse transcription-polymerase chain reaction (RT-PCR) test for detecting the Nucleocapsid gene was also conducted via the health center [10], and both were positive. The FilmArray respiratory panel detected no other respiratory pathogens.

She complained of abdominal pain but was not diagnosed with premature rupture of the membranes. Obstetric examinations revealed a cephalic presentation of a normally grown fetus with a reassuring fetal heart rate pattern. The cervical os was 3.0-cm open with 50% effacement. Antibiotic therapy was initiated based on suspicion of intrauterine bacterial infection. Blood tests showed lymphocytopenia and mildly elevated D-dimer levels, and biochemical tests revealed an increase in the inflammatory response and a decreased thymus and activation-regulated chemokine (TARC) value of 47.5 pg/mL. (Supplementary Table 1). Chest computed tomography images obtained on admission showed local distributions of infiltrations and ground-glass opacities in the subpleural areas of the bilateral lower lobes (Fig. 1). The SpO₂ (under room air) was approximately 93%. Her COVID-19 severity was judged to be moderate. C&I treatment was approved to attenuate the severe progression of COVID-19 under emergency use permission during the 5th epidemic in 2021. We expected that the C&I administration to this patient might prevent the severe progression of pneumonia. On the other hand, we also considered the features of monoclonal antibody drugs in terms of pregnancy (including AU TGA and US FDA pregnancy categories) and lactation (Supplementary Table 2). After conducting the discussion regarding advantage (i.e., attenuation of disease severity) and disadvantage (e.g., AU TGA and US FDA pregnancy categories not available), we decided to treat her with C&I. We provided adequate verbal and written explanations to the patient/her husband and obtained written consent for the MAT administration. C&I was intravenously administered at a single dose for 50 min to reduce disease severity. No adverse reactions (including infusion reactions) were observed after the C&I administration.

On the second day of hospitalization, her fever gradually broke, along with a gradual resolution of cough, malaise, and anorexia (Fig. 2). The abdominal pain on admission was mild. Tests examining membrane rupture (Check PROM™) were negative. On the fifth day, however, the patient went into labor. The SpO₂ (under room air) was gradually recovered (Fig. 2). These clinical manifestations suggested the improvement in COVID-19. We attempted to conduct vaginal delivery rather than cesarean section after considering the choice, since she was a full-term laboring woman without respiratory distress, and her last delivery was complete about 3 years. We brought her to a delivery room with negative pressure conditions, which had been originally built-in: all staff members in the room wore full personal protective equipment (including particulate respirator type N95 and double gloves). The water broke spontaneously about 1 h after the labor onset: a 2.868 kg male newborn was delivered 20 min after the water broke. Apgar scores were 8/8 at 1/5 min after birth. After delivery, her SpO₂ was maintained at ≥95% (under room air). Fig. 2 indicates the clinical course regarding perinatal patient. She required no oxygen supplementation during the perinatal period.

The neonate was isolated and separated from his mother. The newborn had a good and stable condition. Using nasopharyngeal specimens collected immediately after birth and 48 h later, the RT-loop-mediated isothermal amplification (LAMP) test (Loopamp™ SARS-CoV-2 Detection Kit) for detecting the RNA-dependent RNA polymerase/Nucleocapsid genes in the hospital, as well as the real-time RT-PCR test via the health center, were all negative. The newborn showed no signs (including fever or respiratory distress). The mother was placed in the same room with the newborn 10 days after her symptoms developed, and 3 days after her symptoms disappeared, and breastfeeding was started. She hugged her newborn 2 weeks after onset (when the mother’s isolation period had expired). The patient and her newborn were discharged after the isolation period was completed. Thirty days after birth, the infant weighed 4.024 kg: the mother’s pulmonary shadows had improved. The mother and infant had good health status.

3. Discussion

Since the spread of the COVID-19 pandemic across Japan, we have accepted the hospitalization of more than 100 patients. Of these patients, 3 had a gestational age of 30 weeks or more; 2 cases (including this one) resulted in delivery during the treatment period against
COVID-19. We performed a literature review of perinatal cases of COVID-19 in Japan [11–13], along with the first report of a 37-week pregnant woman with COVID-19 pneumonia who delivered a male newborn through a cesarean section in 2020 [14] (Table 1). We searched for related articles by entering keywords “casirivimab, imdevimab, pregnant” into the PubMed database (https://pubmed.ncbi.nlm.nih.gov/), and only one report described 2 cases of childbirth after treatment with C&I from the US in December 2021 [15]. This report documented that two moderate COVID-19 pregnant women (one in the second trimester and another in the third trimester) treated with C&I did not progress to severe disease and did not experience an adverse drug reaction. Additionally, in 4 case series of maternal MAT in pregnancy, there was no evidence of pregnancy complications or treatment failure: all patients avoided progression to severe disease and none required additional COVID-19-related medical visits and hospitalizations [16]. To the best of our knowledge, this is the first Japanese report where treatment with C&I attenuated the COVID-19 severity and led to successful vaginal delivery.

MAT agents have been administered to patients with rheumatoid arthritis for approximately 20 years. In contrast, interleukin (IL)-6 inhibitors have been shown to improve survival among severely ill patients with COVID-19 [17]. While etanercept (ETN), a TNF-α inhibitor that is administered to treat patients with rheumatoid arthritis, has a low incidence of fetal transfer in humans [18], infliximab (IFX) is transferable to fetuses since IFX is detected in the blood specimens of postnatal infants [19]. However, several epidemiological studies have revealed that TNF-α inhibitors can be used safely and continued during the entire pregnancy period in limited cases [6–9]. Placental C&I transfer, as well as their effects on intrauterine fetal exposure, are not yet known. Therefore, the outcomes of mothers and infants receiving MAT need to be monitored carefully for a long period.

COVID-19-associated pneumonia may become more severe during late pregnancy compared to the non-pregnant population [20,21]. TARC is a C–C motif chemokine 17 responsible for trafficking T helper 2 cells into sites of allergic inflammation. Recent study [22] has suggested the role of serum TARC in allergic asthma via contributing to mast cell and eosinophilic inflammation. Her serum TARC level (47.5 pg/mL) on admission was low, suggesting severe progression. Serum TARC levels of 87.5 pg/mL or less are associated with severe situations [23].

Casirivimab and imdevimab are large proteins with molecular weights of over 145,000 Da and 144,000 Da, respectively [24] (Supplementary Table 2). ETN, with a molecular weight of approximately 150,000 Da and adalimumab (ADA), a TNF-α inhibitor, with a molecular weight of about 148,000 Da, have lower breast milk concentrations than

Table 1
Literature review concerning Japanese pregnant women with COVID-19 pneumonia.

| Reference number | Onset | Mother age (year-old) | Gestational age | Past delivery | Comorbidity | Chest image findings | Respiratory care | Current delivery | Apgar score(s) at 1 & 5 min | Specific treatment | SARS-CoV-2 test for neonate | SARS-CoV-2 test using breast milk |
|------------------|-------|----------------------|----------------|--------------|-------------|----------------------|----------------|----------------|--------------------------|----------------|-----------------------------|-------------------------------|
| [14]             | Apr 2020 | 20s                  | 37 weeks & 6 days | Present | Not available | Infiltrations/ground-glass opacities in both lungs | Oxygen supplementation on postpartum | Cesarean section | 8 & 6 | Lopinavir/ritonavir | Negative | Negative | Negative |
| [12]             | 2020   | 30                   | 36 weeks        | Not available | Healthy | Acute respiratory distress syndrome | Extracorporeal membrane oxygenation | Cesarean section | 8 | Favipiravir, tocilizumab, & methylprednisolone | Negative | Not available | Not available |
| [11]             | 2020   | 30                   | 36 weeks        | Not available | Healthy | Infiltrations/ground-glass opacities in both lungs | Extracorporeal membrane oxygenation | Cesarean section | 8 & 6 | Lopinavir/ritonavir, remdesivir, tocilizumab, & dexamethasone | Negative | Not available | Not available |
| This case        | Aug 2021 | 39                  | 36 weeks & 6 days | Present | Healthy | Infiltrations/ground-glass opacities in both lungs | Ventilator | None | None | Casirivimab/imdevimab | Negative | Negative |

Fig. 2. Clinical course of a perinatal COVID-19 patient receiving combined casirivimab and imdevimab treatment followed by conducting vaginal delivery. BT, body temperature; SpO₂, percutaneous saturation of oxygen; LDH, lactate dehydrogenase; CRP, C-reactive protein; WBC, white blood cell count; Lymph, lymphocyte count; w, weeks; d, days.
in serum. Both agents can be applied as beneficial administration during lactation because no adverse events are observed even when the administration of ETN or ADA is continued during lactation [18,25]. C&I has similar molecular weights: drugs’ excretion into breast milk is expected to be limited and small. Additionally, the drugs secreted into breast milk are likely to be destroyed in the infant’s gastrointestinal tract; the absorption by infants and their impacts are expected to be minimal. C&I is expected to be used as beneficial administration, which may overcome the risks during lactation. Thus, we started breastfeeding for the newborn after the mother’s isolation period had expired.

The risk of infection to newborn associated with vaginal delivery needs to be considered. Recent study [26] has demonstrated unlikely SARS-CoV-2 transmission during vaginal delivery, since no virus particles were detected in vaginal swabs of the pregnant women. In this case, RT-LAMP and RT-PCR test results were negative for the newborn. Additionally, because of the COVID-19-transmission possibility through breast milk or bottles, we did not start breastfeeding until her isolation period had finished. SARS-CoV-2 was not detected in the breast milk of mothers with COVID-19 in another report [14] (Table 1). When the separation period of the mother and child is prolonged, we may consider the option of initiating breastfeeding and performing the RT-LAMP/RT-PCR using breast milk.

We herein report the case of a pregnant woman who showed improvement in COVID-19 pneumonia after MAT administration, resulting in successful vaginal delivery. Early diagnosis and treatment of pregnant women with COVID-19 are important. Therefore, infectious diseases doctors and/or obstetricians should be aware of the MAT option administered to perinatal COVID-19 women to reduce disease severity.

Declaration of competing interest
None.

Funding
None.

Authorship statement
All authors met the ICMJE authorship criteria.

Conceptualization – E.O. and T.T.

Patient Care and Treatment – H.G., H.U., A.M., S.T., R.N., and T.H.

Formal Analysis – E.O.

Writing – Original Draft Preparation – E.O.

Writing – Review and Editing – T.T.

All authors read and approved the final manuscript.

Informed consent

The authors obtained written informed consent for submission and publication of this case report (including the clinical data and images) from the patient and her husband.

Acknowledgement

The authors wish to thank Editage (www.editage.jp) for English language editing.

Appendix A/B. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.jiac.2022.02.023.
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