Short Communication

Apparent Life-Threatening Event in an Infant with SARS-CoV-2 Infection

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SUMMARY: The 2019 novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused a global outbreak of infection. In general, children with coronavirus disease-2019 have been reported to show milder respiratory symptoms than adult patients. Here, we have described a case of a SARS-CoV-2-infected infant who presented to our hospital with a severe episode of an apparent life-threatening event (ALTE). An 8-month-old, otherwise healthy female infant presented to our hospital because of a sudden cardiopulmonary arrest. Approximately 1 h before this episode, the patient showed no symptoms, except a worse humor than usual. On arrival at our hospital, the patient had severe acidosis, but there were no clear signs of inflammatory response. Chest computed tomography showed weak consolidations in the upper right lung and atelectasis in the lower left lung. No signs of congenital heart disease or cardiomyopathy were observed on echocardiography, and no significant arrhythmia was observed during the clinical course. However, SARS-CoV-2 RNA was detected by real-time reverse transcription polymerase chain reaction in tracheal aspirate and urine samples. Although the assessment of further similar cases is indispensable, this case suggests that SARS-CoV-2 infection may be an underlying factor in the pathophysiology of ALTE.

The 2019 novel coronavirus, severe acute respiratory syndrome coronavirus (SARS-CoV-2), has caused a global outbreak of infection (1–3). In general, children with coronavirus disease-2019 (COVID-19) have been reported to show milder respiratory symptoms than adult patients (4). Moreover, asymptomatic infections have been more commonly reported in children (5). However, several severe cases have recently been reported in younger children, especially infants (6).

An Italian guideline defines an apparent life-threatening event (ALTE) in infants as an episode characterized by a combination of apnea, color change, marked change in muscle tone, choking, or gagging (7). In infants, lower respiratory infections are one of the underlying conditions of an ALTE (7,8). Here, we have described a case of a SARS-CoV-2-infected infant who presented with a severe episode of an ALTE.

An 8-month-old girl presented to our hospital because of a cardiopulmonary arrest. The mother called an

ambulance when she noticed that the child was pale, did not breathe in the prone position, and was unresponsive to stimulation. Approximately 1 h before calling the ambulance, the mother engaged in face-to-face interactions with the child while she was feeding her. At that time, the infant showed no signs or symptoms, except a worse humor than usual. The patient had a pulseless electrical activity when she was taken in the ambulance and was immediately transferred to our hospital after intratracheal intubation by an emergency physician. Recovery of spontaneous circulation was accomplished through cardiopulmonary resuscitation with an intraosseous infusion of adrenaline and sodium bicarbonate. On arrival at our hospital, blood gas analysis using a bone marrow sample revealed severe acidosis (pH 6.525, pCO₂ 94.8 mmHg, BE-27.1 mmol/L). The patient was the only child of healthy non-consanguineous Japanese parents and did not have a family history of febrile seizures, epilepsy, heart disease, or sudden death in childhood. The patient had been vaginally delivered at full term and weighed 3,016 g. The metabolic screening test performed during the neonatal period showed no abnormalities. The patient's development was appropriate for her age, and the patient had no previous history of respiratory symptoms and febrile seizures. Immunizations were performed on schedule without significant adverse events, and the patient received the BCG vaccine at 5 months of age.

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Fig. 1. Chest (A, B, and C) and head (D) computed tomography scans of the patient on admission. A and B, arrows indicate weak consolidations in the upper right lung. C, circle indicates atelectasis in the lower left lung.

Analysis of the peripheral blood on admission revealed the following: white blood cell count, $5.39 \times 10^3/\mu\text{L}$; hemoglobin level, 10.2 g/dL; and thrombocyte count, $234 \times 10^3/\mu\text{L}$. Blood tests revealed no clear sign of inflammation as the levels of serum C-reactive protein and procalcitonin were <0.1 mg/dL and 0.03 ng/mL, respectively. The serum immunoglobulin G (IgG) level was 114 mg/dL, but the levels of CD3+ T cells, CD19+ B cells, and CD56+ NK cells in the peripheral blood were within the normal range. Viral antigen tests using nasopharyngeal aspirate samples revealed negative results for respiratory syncytial and influenza virus infections. After recovery of spontaneous circulation, the electrocardiogram showed a mildly prolonged QT interval ($\text{QTc} = 456$ ms), but no significant arrhythmia was observed in the clinical course of infection. Echocardiography indicated a normal left ventricular ejection fraction, suggesting that the involvement of congenital heart disease or cardiomyopathy was unlikely. Chest computed tomography (CT) showed weak consolidations in the upper right lung (Fig. 1 A and B) and atelectasis in the lower left lung (Fig. 1C). Moreover, head CT revealed signs of brain edema with ambiguous grey-white differentiation and narrow cerebral ventricles without bleeding (Fig. 1D), suggesting hypoxic encephalopathy. Consequently, systemic hypothermia was immediately induced using a ventilator to protect her brain.

Real-time reverse transcription (RT) polymerase chain reaction (PCR) analysis for SARS-CoV-2 was performed (9) using the tracheal aspirate sample (Fig. 2A) with N (P28706–28814) and N2 (P29125–29263) primers (Fig. 2B). The tracheal aspirate sample was treated with 0.75% dithiothreitol in phosphate-buffered saline for 10 min and subsequently treated with DNases for 10 min. Viral RNA was extracted using the QIAamp Viral RNA Mini Kit (Qiagen, Venlo, Netherlands). SARS-CoV-2 RNA was detected using AgPath-ID™ One-Step RT-PCR Reagents (AM1005, Applied Biosystems, Bedford, MA, USA) on a CobasZ480 (Roche, Pleasanton, CA, USA). Nested PCR was performed using the same sample. The first PCR test was performed using sense (P28185–18204) and anti-sense (P29548–29567) primers, and the second PCR test was performed using the N2 primer (Fig. 2B). Each PCR test included 40 amplification cycles.

Considering the weak pulmonary consolidations observed on chest CT, we performed real-time RT-PCR analysis for SARS-CoV-2 using the tracheal aspirate sample. Real-time RT-PCR analysis using the N primers (cycle threshold [Ct]: 29.1 and 29.8) and the N2 primers (Ct: 27.7 and 28.2) revealed positive results (Fig. 2C). A nested RT-PCR test was performed to verify the positive real-time RT-PCR results using the same sample. The expected fragment size (158 bp) of the second PCR product was observed (Fig. 2D). A positive reaction

Fig. 2. RT-PCR analysis of SARS-CoV-2. A, schematic representation of RT-PCR analysis. B, primers and probes for RT-PCR analyses. Numbers indicate nucleotide sequence of viral RNA (GenBank MN908947.3). Arrows indicate primers for real time and nested RT-PCR and boxes indicate probes for real time RT-PCR. Initial ATG and stop codon of nucleocapsid phosphoprotein are highlighted. C, amplification curves of real time RT-PCR analysis using a tracheal aspirate on admission. D, nested RT-PCR analysis using a tracheal aspirate on admission. Left panel indicates first PCR, while right panel indicates second PCR. Arrowheads indicate specific PCR samples.

was also confirmed through real-time RT-PCR analyses using tracheal aspirate and urine samples obtained on day 4 (data not shown).

In the present case report, an 8-month-old female infant with sudden onset of cardiopulmonary arrest was found to be infected with SARS-CoV-2. We performed an RT-PCR for SARS-CoV-2 after observing pulmonary consolidations on chest CT. However, the rapid progression of respiratory symptoms due to COVID-19-associated pneumonia was unlikely to be the direct cause of cardiopulmonary arrest since the patient had no symptoms of respiratory infection, except for atelectasis, and the pulmonary consolidations were extremely weak at the time of admission. In a previous study, 50%–58% ALTE cases were associated with comorbidities such as seizures, metabolic disease, arrhythmias, congenital heart diseases, and infections (7). However, in the present case, these comorbidities, except SARS-CoV-2 infection, were unlikely to be the cause of the ALTE, given the patient's medical history and findings of head CT, electrocardiography, and echocardiography. Furthermore, a case of an ALTE with severe apnea attributable to human coronavirus HCoV-229E infection has previously been reported (10). In this

case report, RT-PCR successfully detected HCoV-229E in a 4-month-old infant with repeated apnea episodes in a short time (10).

Based on this report, although apnea episodes were not observed in the present case, it is conceivable that any rapidly progressive comorbidities due to SARS-CoV-2 infection, such as apnea, may underly cardiopulmonary arrest.

In summary, although the assessment of similar cases is indispensable to draw a conclusion, the case presented here suggests that SARS-CoV-2 infection is a candidate underlying factor in the pathophysiology of ALTE and sudden infant death syndrome.

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Conflict of interest None to declare.

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