Case Report

Necrotizing Enterocolitis in a 34-Week Premature Infant with COVID-19

Mary K. Mannix,1 Danielle Blood,2 Oscar G. Gomez-Duarte,1 and Lauren Davidson2

1Division of Infectious Diseases, Department of Pediatrics, University at Buffalo, the State University of NY, Buffalo, NY, USA
2Sister’s Hospital, Catholic Health System, Buffalo, NY, USA

Correspondence should be addressed to Lauren Davidson; ldavidson@chsbuffalo.org

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Coronavirus disease 2019 (COVID-19) is a viral respiratory infection caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), a betacoronavirus, that has spread worldwide reaching pandemic proportions [1]. The COVID-19 pandemic is already a leading cause of morbidity and mortality worldwide with an estimated number of deaths above 3 million according with the John Hopkins dashboard (https://coronavirus.jhu.edu/map.html). The number of deaths due to COVID-19 in the US is the highest in the world and reaching 600,000. Information on the effect of COVID-19 among newborn infants indicates that the majority of infected infants, including neonates in nurseries and Neonatal Intensive Care Units (NICUs), are believed to acquire SARS-CoV-2 by horizontal transmission, and most of them have had asymptomatic or mildly symptomatic infections [2, 3].

Extrapulmonary manifestations of COVID-19 or of multisystem inflammatory disease in children associated to COVID-19 (MIS-C) include gastrointestinal symptoms, and diarrhea, vomiting, and abdominal pain are the most common manifestations [4, 5]. Limited information is available on severe gastrointestinal disorders among premature and full-term newborns. The objectives of this case report are to describe a case of a 34 weeks gestational age premature infant born diagnosed with COVID-19 and necrotizing enterocolitis (NEC), shortly after birth, and to briefly review the literature on the role of COVID-19 on gastrointestinal disorders in pediatrics.

1. Introduction

Coronavirus disease 2019 (COVID-19) is a viral respiratory infection caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), a betacoronavirus, that has spread worldwide reaching pandemic proportions [1]. The COVID-19 pandemic is already a leading cause of morbidity and mortality worldwide with an estimated number of deaths above 3 million according with the John Hopkins dashboard (https://coronavirus.jhu.edu/map.html). The number of deaths due to COVID-19 in the US is the highest in the world and reaching 600,000. Information on the effect of COVID-19 among newborn infants indicates that the majority of infected infants, including neonates in nurseries and Neonatal Intensive Care Units (NICUs), are believed to acquire SARS-CoV-2 by horizontal transmission, and most of them have had asymptomatic or mildly symptomatic infections [2, 3].

2. Case Presentation

A 27-year-old G1P0 mother presented to the hospital in preterm labor with preterm premature rupture of membranes (PPROM) at 33 1/7 weeks gestation. Pregnancy was
Necrotizing enterocolitis is a significant cause of morbidity and mortality among infants in the NICU. Although necrotizing enterocolitis continues to afflict neonates of all sizes and gestational age, it is much more commonly seen in infants born less than 1500 g in weight and less than 28 weeks in gestation [8]. The pathophysiology of NEC is multifactorial, resulting in acute inflammation and invasion of the intestinal wall. Classic risk factors for NEC include premature rupture of membranes, extreme prematurity, very-low-birth-weight (VLBW) infants, exposure to medications including antibiotics, and exposure to formula [9]. A study conducted by Sharma et al., including over 200 infants with NEC, found that the mean age of onset was around 20 days of life [10]. Our patient was born at 34 weeks gestation, was over 2,000 g at the time of birth, and had signs of NEC at 30 hours of life which is much earlier than frequently
seen with NEC. There is a likelihood that COVID-19 in this premature infant contributed directly or indirectly to NEC. Only one case of an NEC-like disorder was reported in the literature in a 7-week-old term male with confirmed pneumatisis intestinalis who was also positive for COVID-19 [11].

Coronavirus infection in human subjects is not limited to the respiratory tract. There was a reported cluster of NEC cases associated with infections due to coronavirus-like agents in the early 1980s. Histopathology evaluation of intestinal specimens revealed coronavirus-like particles within intracytoplasmic vesicles of damaged mucosal cells of the small intestine, appendix, and colon [12, 13]. In addition to NEC, there have been reports of gastrointestinal disorders associated with COVID-19 or MIS-C in pediatric patients that are manifested with nausea, vomiting, diarrhea, and abdominal pain [4, 5, 14]. Appendicitis in children has been associated with acute presentations of COVID-19 [15]. Furthermore, the severe acute respiratory syndrome caused by the SARS coronavirus in China back in 2003 was associated with gastrointestinal disorders including diarrhea [16]. How SARS-CoV-2 may induce severe inflammation leading to NEC in a small number of infants is a question that remains unanswered. The gut microbiome may be the link between COVID-19 and gastrointestinal disorders [17], yet it is unclear whether gut microbiome dysbiosis may explain the severe gastrointestinal manifestations during COVID-19 in some patients [18]. Overall, it is likely that acute inflammation in the gastrointestinal tract during or after SARS-CoV-2 infection in association with gut microbiome changes may lead to severe gastrointestinal disorders in infants, including NEC. One limitation of this report was the lack of SARS-CoV-2 PCR testing of the infant's stool. A positive result would have corroborated the association of gastrointestinal SARS-CoV-2 infection with NEC in this infant.

4. Conclusions

This was a formula-fed premature newborn infant who shortly after birth had gastric feed intolerance and AXR imaging consistent with NEC. This case of NEC is unusual because the age of onset was too early, the patient was not a

| Parameters | Values DOL1 0 | Values DOL1 2 | Reference values |
|------------|--------------|---------------|-----------------|
| WBC        | 12.3         | 8.3           | 7.0–30.0 × 10^3/μL |
| RBC        | 5.47         | 4.71          | 4.0–7.0 × 10^6/μL  |
| HGB        | 20.3         | 17.4          | 14.5–22.5 g/dL    |
| HCT        | 58.2         | 50.5          | 45.0–67.0%        |
| MCV        | 106.5        | 107.2         | 95.0–121.0 fl.    |
| MCH        | 37.1         | 37.0          | 31.0–37.0 pg      |
| MCHC       | 34.9         | 34.6          | 29.0–37.0 g/dL    |
| RDW        | 15.9         | 16            | 13.0–18.0%        |
| PLTS       | 353          | 307           | 150.0–300.0 10^3/μL |
| MPV        | 8.4          | 10.0          | 29.0–37.0 g/dL    |
| Neutrophils (%) | 73     | 27            | 30–60%           |
| Bands (%)  | 0            | 17            | 0–9%             |
| Lymphocytes (%) | 18   | 43            | 25–50%           |

DOL: day of life.

Figure 1: Abdominal x-rays of the premature infant. (a) Image obtained at 30 h of age. Arrow indicates the area of pneumatisis intestinalis. (b) Image obtained at 36 h of age. Upper arrow points to one area of pneumoperitoneum, and the lower arrow points to an area of pneumatisis intestinalis.
very-low-weight premature infant, and the infant had no low gestational weight. The fact that the neonate had COVID-19 at the time NEC was diagnosed suggests that SARS-CoV-2 infection was likely associated with this severe gastrointestinal disorder.

**Data Availability**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

**Consent**

Informed consent was obtained from the patient’s parent for case report publication.

**Conflicts of Interest**

The authors state that they have no conflicts of interest to declare.

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