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LETTER TO THE EDITOR

Pediatric coronavirus (COVID-19) death in a child with cyclic neutropenia

To the Editor:

Cyclic neutropenia is a condition of intermittent and severe neutropenia (absolute neutrophil count [ANC] < $0.50 \times 10^3/\mu l$) accompanied by symptoms of fevers, mouth ulcerations, and recurrent bacterial infections. Infections require prompt treatment with antibiotics and often granulocyte colony-stimulating factor.[1,2] Cyclic neutropenia is inherited in an autosomal dominant fashion secondary to pathologic variants of the *ELANE* gene, which encodes neutrophil elastase. The resulting abnormal enzyme damages developing neutrophils, leading to a shortened neutrophil lifespan.[2]

The incidence of coronavirus disease 2019 (COVID-19) and severity of disease in children is less than that of adults.[3] Most children with COVID-19 have mild symptoms that can be managed supportively, but severe consequences may include thromboses, respiratory failure, and multisystem inflammatory syndrome in children (MIS-C).[4,5] Neurologic symptoms with COVID-19 have also been published in pediatric cases including new-onset febrile or afebrile seizures and status epilepticus.[6,7]

The mechanism of an apparent innate protection against infection in children is not fully understood. Overall, children tend to have fewer co-morbidities and less cumulative environmental toxic exposures compared to adults, as well as more active immune systems.[8] It is known that as we age, our innate and adaptive immune responses dampen via thymic atrophy,[9] and that low CD4+ T cells have been associated with increased severity of disease from COVID-19 infection in adults.[10] Therefore, children with diminished immune capabilities (whether adaptive or innate responses) could potentially be at risk for severe disease and worse outcomes from COVID-19 as well. Here, we present the first reported COVID-19-related death in a pediatric patient with cyclic neutropenia, demonstrating a potential vulnerable population in the current pandemic.

The female child was 3-year old who was undergoing work-up for presumed cyclic neutropenia that died acutely and whose post-mortem examination was significant for COVID-19 infection and pneumonitis. The patient's father had confirmed cyclic neutropenia and patient herself had history of recurrent ear infections, oral ulcers, febrile seizures, and documented low ANC on several occasions. She had been referred to a hematologist for diagnostic workup and treatment of cyclic neutropenia 2 weeks prior to her death.

On the day of presentation, patient had a febrile seizure and was brought to her local emergency department (ED). She was postictal, febrile, hypoxemic, and tachycardic upon arrival. Full laboratory work-up is shown in Table 1, and significant findings include leukopenia, neutropenia, hypoalbuminemia, hypochloremia, and hyponatremia. C-reactive protein, procalcitonin, and lactic acid inflammatory markers were extremely elevated. Nasopharyngeal COVID-19 polymerase chain reaction (PCR) was positive. Computed tomography of the head showed no abnormal findings, and chest X-ray showed clear lung fields, normal pulmonary vasculature, and normal heart size. Approximately 3 hours after ED arrival, her respirations became agonal and she developed bradycardia evolving into asystole. She received multiple rounds of cardiopulmonary resuscitation. Return of spontaneous circulation was not achieved, and time of death was pronounced an hour after code began.

An autopsy revealed significant pneumonitis consistent with viral toxicities as well as diffuse alveolar damage with hyaline membranes noted. Acute inflammation was noted in the terminal ileum and cecum. Central nervous system (CNS) evaluation noted scattered immature neuronal clusters in the amygdala and a single cluster of left hippocampal heterotopic granule cells of unknown significance. Microbiology evaluation revealed postmortem bacterial colonization/contaminants that were not contributory to death. Viral panel was only positive for COVID-19 antigen. The cause of death in this patient with cyclic neutropenia was deemed "complications of novel COVID-19 infection." Genetic testing confirmed heterozygous ELANE mutation in the patient's twin sister and 9-year-old sister on subsequent follow up.

Current literature reviewing histopathology and gross autopsy findings in those who have died from COVID-19 show pulmonary congestion and hyaline membrane formation with diffuse alveolar damage to be a recurring finding, similar to our patient.[11] CNS and gastrointestinal findings related to COVID-19 during autopsy appear to be widely variable at the time of writing of this letter to the editor.

Children with cyclic neutropenia are at higher risk for bacterial infections, but the role neutrophils play in viral immunity is less well defined. It has been suggested that neutrophils enhance antiviral defenses by interaction with other immune cell populations, virus internalization and killing mechanism, cytokine release, oxidative burst, and creation of neutrophil extracellular traps.[12,13] Studies surveying immune responses in severe presentations of COVID-19 such as MIS-C have noted upregulation of neutrophils and monocytes, suggesting the inflammatory innate immune response may be critical to the pathogenesis of and/or defense against COVID-19/MIS-C.[14]

While the exact contribution of neutropenia to the terminal disease process in our case is uncertain, it is of upmost importance for children

TABLE 1 Lab values obtained on ED admission of 3-year-old female patient with cyclic neutropenia and acute COVID-19 infection

Labs obtained on admission	Patient's lab values	Reference range
White cell count (x$10^3/\mu$l)	2.97	6.0–17.5
Hemoglobin (g/dl)	11.4	9.5–14.0
Platelet count (x$10^3/\mu$l)	260	182–369
Absolute neutrophil count (x$10^3/\mu$l)	0.19	1.56–6.13
Absolute lymphocyte count (x$10^3/\mu$l)	1.3	1.18–3.74
Sodium (mEq/L)	126	136–145
Potassium (mEq/L)	4.8	3.4–4.7
Chloride (mEq/L)	91	98–107
Carbon dioxide (mEq/L)	18.6	17–35
Blood urea nitrogen (mg/dl)	13	5–18
Creatinine (mg/dl)	0.57	0.2–0.5
Glucose (mg/dl)	136	60–100
Albumin (g/dl)	3.3	3.8–5.4
Aspartate aminotransferase (U/L)	83	8–37
Alanine aminotransferase (U/L)	25	14–59
Total bilirubin (mg/dl)	0.6	0.2–1.0
Anion gap (mEq/L)	21.2	5–15
C-reactive protein (mg/dl)	34.7	0.00–0.90
Lactic acid (mmol/L)	10.1	0.4–2.0
Procalcitonin (ng/ml)	97.26	0.00–0.10
STREP group A rapid antigen	Negative	Negative
STREP group A DNA amplification	No Group A Strep detected	
Influenza antigen A rapid	Negative	Negative
Influenza antigen B rapid	Negative	Negative
SARS CoV 2 PCR	Detected	Not detected

with neutropenia to be evaluated by a medical professional at first sign of illness, with attention paid to COVID-19 as a potential etiology.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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