PEDIATRIC CORONAVIRUS (COVID-19) DEATH IN A CHILD WITH CYCLIC NEUTROPENIA

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Abstract

We present the case of a 3-year-old female with cyclic neutropenia and history of febrile seizures who died acutely from coronavirus disease 2019 (COVID-19). While most children with COVID-19 infection are asymptomatic or have mild symptoms, there may be increased risk of severe disease in immunocompromised children. To the best of our knowledge, this is the first reported case of a COVID-19-related death in a pediatric patient with cyclic neutropenia.

pediatric coronavirus (covid-19) death in a child with cyclic neutropenia

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COVID-19	Coronavirus disease 2019
ANC	absolute neutrophil count
G-CSF	Granulocyte colony-stimulating factor
MIS-C	Multisystem inflammatory syndrome in children
ED	Emergency department
PCR	Polymerase chain reaction
CT	Computed tomography
CNS	Central nervous system

ABSTRACT

We present the case of a 3-year-old female with cyclic neutropenia and history of febrile seizures who died acutely from coronavirus disease 2019 (COVID-19). While most children with COVID-19 infection are asymptomatic or have mild symptoms, there may be increased risk of severe disease in immunocompromised children. To the best of our knowledge, this is the first reported case of a COVID-19-related death in a pediatric patient with cyclic neutropenia.

INTRODUCTION

Cyclic neutropenia is a rare hematologic condition defined by intermittent and severe neutropenia [absolute neutrophil count (ANC) <0.50 x $10^3/\mu L$] that occurs in a predictable pattern, often every 21 days. The decline in ANC is frequently accompanied by classic symptoms of fevers, mouth ulcerations and recurrent bacterial infections. Fevers and infections in this population require prompt attention and treatment with antibiotic therapy and often granulocyte colony-stimulating factor (G-CSF).[1,2] Cyclic neutropenia is inherited in an autosomal dominant fashion secondary to pathologic variants of the ELANE gene. ELANE encodes neutrophil elastase, an enzyme that is required for neutrophil function. In the case of cyclic neutropenia, the abnormal enzyme is not packaged correctly and damages neutrophils during their development, leading to a shortened neutrophil lifespan.[2]

There is still much to learn about COVID-19 in children as well as which children are at risk for severe disease. The incidence of COVID-19 in children is less than that of adults, however, with improved screening capabilities and testing availability, we are seeing a significant increase in pediatric cases. Even with this increase, severe disease appears to be more prevalent in adults than children.[3]Most children with COVID-19 have mild symptoms including fever, cough, rhinorrhea, sore throat, diarrhea and/or vomiting which can be managed supportively. Severe consequences of this disease may include thromboses, respiratory failure and Multisystem Inflammatory Syndrome in Children (MIS-C), which may lead to pediatric intensive care.[4,5] Neurologic symptoms have also been published in pediatric case reports of new onset febrile or afebrile seizures or status epilepticus in the setting of COVID-19.[6,7]

The mechanism of an apparent innate protection against infection in children is not yet 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] For example, 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 adult populations.[10] Therefore, it stands to reason that 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. Below 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.

CASE DESCRIPTION

We present a 3-year-old twin female who was undergoing initial 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 a confirmed diagnosis of 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 just two weeks prior to her untimely death.

On the day of presentation, patient had sustained a febrile seizure at home and was brought to her local emergency department (ED). Upon arrival, she was post-ictal, febrile and tachycardic with an oxygen saturation of 90% on room air. Full laboratory work-up is shown in table 1, however significant findings include leukopenia (2.97 x10^3/μL) and associated neutropenia (ANC 0.19 x10^3/μL). Electrolytes were notable for hypoalbuminemia (3.3 gm/dL), hypochloremia (91 mEq/L) and hyponatremia (126 mEq/L). Inflammatory markers were significant for elevated C-reactive protein (34.7 mg/dL), procalcitonin (97.26 ng/mL) and lactic acid (10.1 mmol/L). COVID-19 PCR was positive from a nasopharyngeal swab upon arrival. CT head showed no abnormal findings and chest X-ray showed clear lung fields, normal pulmonary vasculature and normal heart size. Approximately 3 hours after arrival to the ED, the child had significant and rapid clinical deterioration. Her respirations became agonal and she developed bradycardia evolving into asystole. The patient received multiple rounds of cardiopulmonary resuscitation. Return of spontaneous circulation was not achieved, and time of death was called an hour after her initial code event.

An autopsy performed by the state medical examiner revealed multiple important findings. The lungs had significant pneumonitis consistent with viral toxicities as well as diffuse alveolar damage with hyaline membranes noted. There was acute inflammation noted in the gastrointestinal tract located at the terminal ileum and cecum. Central nervous system (CNS) evaluation did not show any overt findings of encephalitis or meningitis but noted scattered immature neuronal clusters in the amygdala and a single cluster of left hippocampal heterotopic granule cells. Microbiology evaluation revealed postmortem bacterial colonization/contaminants that were not contributory to death. Viral panel was negative except for a positive COVID-19 antigen test. The cause of death in this patient with cyclic neutropenia was determined to be "complications of novel COVID-19 infection."

On subsequent follow-up, the patient's twin sister and 9-year-old sister were both confirmed to have a heterozygous ELANE mutation, which causes cyclic neutropenia and is consistent with their father's diagnosis.

DISCUSSION

As the COVID-19 pandemic evolves, new complications and treatments of the infection are continually emerging, as well as realizations of risk factors for severe disease. While a vast majority of children can be managed with conservative measures and isolation, there are potentially vulnerable populations of children who may exhibit severe manifestations of this disease.

We know children with cyclic neutropenia are at an innately higher risk for recurrent bacterial infections, though neutrophils may also play a prominent role in viral infections. Neutrophils have been implicated in antiviral immunity through cytokine release, reactive oxygen species and through creation of neutrophil extracellular traps.[11]Therefore, those who are severely neutropenic may be at an increased risk of severe viral illness as well.

Current literature reviewing histopathology and gross autopsy findings in those who have died from COVID-19 is still evolving, however some patterns in pulmonary findings are emerging. One cohort study showed the most common pulmonary finding included significant pulmonary congestion and hyaline membrane formation with diffuse alveolar damage, similar to our presented patient.[12] CNS findings related to COVID-19 appear to be widely variable at the time of this writing, and the literature likewise does not appear to have a common gastrointestinal finding at autopsy related to this disease.

While the exact significance of the contribution of neutropenia to the terminal disease process in our case is uncertain, her underlying condition rendered her a high risk for viral respiratory infections in general. It is of upmost importance for children with neutropenia to be evaluated by a medical professional immediately 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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