Childhood B-Cell Acute Lymphoblastic Leukemia Following SARS CoV-2 Infection: A Potential Second "Hit" in Leukemogenesis

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Summary: The Coronavirus Disease 2019 (COVID-19) pandemic has become the worst pandemic in modern history. The lack of prior immunity to the virus has resulted in a high mortality rate, though children have fared better than adults, overall. We present a case of a child who developed B-cell acute lymphoblastic leukemia 1 week following a symptomatic COVID-19 infection. It is possible that this viral infection provided the "second hit" posited to occur in pediatric leukemogenesis as proposed by Dr Greaves, with his initial viral exposure occurring several weeks earlier.

Key Words: ALL, B-ALL, childhood leukemia, B-cell lymphoblastic leukemia, delayed infectious theory, COVID-19, SARS CoV-2

(*J Pediatr Hematol Oncol* 2020;00:000–000)

The severe acute respiratory syndrome corona virus 2 (SARS CoV-2) which causes Coronavirus Disease 2019 (COVID-19), the most devastating global pandemic in 100 years, has infected millions of individuals worldwide. Public health measures implemented to contain the spread of the virus, have included widespread closure of schools, businesses, and restrictions on social gatherings. We recently proposed that the COVID-19 pandemic may also have an impact on the development of childhood acute lymphoblastic leukemia (ALL), the most common form of childhood cancer, due to a reduced exposure of children to other infectious diseases; or that infection with the SARS CoV-2 may provide the "second hit" resulting in an increase in ALL incidence during the pandemic in infected children.[1] We report a patient who was diagnosed with ALL within a very short timeframe following a symptomatic COVID-19 infection.

CASE REPORT

A 9-year-old boy presented with a 1 week history of abdominal pain, diarrhea, progressive respiratory distress and a 2 day history of tactile fevers. On physical examination, he was tachycardic and tachypneic with no other significant findings. His complete blood count (CBC) revealed a white blood cell count 10,500/cumm, hemoglobin 11.1 g/dL, platelet count 234,000/cumm and an absolute neutrophil count 7500/cumm without atypical lymphocytes or lymphoblasts being reported. The lactate dehydrogenase (LDH) was 855 U/L, C-reactive protein > 1800 mg/L and ferritin 455 ng/mL. A nasopharyngeal swab tested positive for COVID-19 by PCR. Chest x-ray showed findings consistent with small airway disease. An ultrasound of the abdomen did not demonstrate hepatosplenomegaly. He was started on high flow oxygen and was subsequently weaned to room air and discharged home in stable condition 2 days later.

Seven days following discharge, he had new complaints of clavicle and hip pain and mild anorexia which led him to be brought for a medical reevaluation. His exam was pertinent for a new finding of splenomegaly palpable 2 cm below the costal margin. His CBC revealed a white blood cell 8,200/cumm, hemoglobin 10.9 g/dL, platelets 153,000/cumm, absolute neutrophil count 4400/cumm with lymphoblasts noted on the peripheral smear. The LDH was 1,586 U/L, and uric acid 4.9 mg/dL. A repeat COVID-19 PCR test was negative. There was near complete replacement of the bone marrow with 95% lymphoblasts which expressed HLA-DR, CD10, CD22, CD19, CD9, CD38, and cTDT by immunophenotyping consistent with a diagnosis of B-cell ALL. There was no expression of CD34 or myeloid markers. Cytogenetics studies demonstrated a balanced translocation involving TCF3 with PBX1 [t(1;19)], isochrome 7, partial deletion of chromosome 6q and gain of RUNX1. He was classified as CNS1. He started induction chemotherapy with vincristine, dexamethasone, peg-asparaginase, and intrathecal cytarabine/methotrexate.

DISCUSSION

The majority of children diagnosed with ALL, have no known predisposing risk factors to develop leukemia, though there is increasing evidence that supports the hypothesis that infectious agents may trigger the development of childhood leukemia.[2–5] The prevailing infectious etiology theory proposes that ALL arises from "2 hits"; a preleukemia clone arising prenatally (first hit) and a "second hit" occurring postnatally, leading to the development of ALL. In this model theorized by Dr Greaves, the "second hit" is delayed exposure to a common infectious agent which the child had not developed any prior immunity to. A proportion of healthy children in the general population, harbor preleukemia cells and if one of these susceptible children is exposed to an infectious agent (second hit), an abnormal immune response may stimulate the proliferation of the preleukemic lymphocyte population. This leads to the development of ALL which manifests clinically.[6,7] As a novel virus which the population lacks immunity to,

Received for publication September 1, 2020; accepted November 18, 2020.

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J.W.T. is supported by the Ring Screw Textron Endowed Chair.

The authors declare no conflict of interest.

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COVID-19 could act as the infectious "second hit" agent.[1] A similar scenario was observed in Milan, Italy between December 2009 to January 2010, where a reported ALL cluster was reported in as little as 4 weeks following the novel avian H1N1 outbreak.[4]

What was striking in our patient, was the very short duration of leukemia-associated symptoms, specifically bone pain and a rapidly rising LDH level. Pediatric ALL patients who present with bone pain as the predominant clinical symptom, typically have a relatively long duration of pain prior to diagnosis; in studies reported by Louvigne and colleagues, Teo and colleagues, Kobayashi and colleagues, and Boccuzzi and colleagues, the median duration of bone pain symptoms were 57, 21, 42 and 20 days, respectively.[8–11] At our own institution, a review of the presenting symptoms of bone pain in ALL cases diagnosed over the past 5 years, identified that the median duration was 28 days.

LDH levels may be elevated in patients with COVID-19, typically in the range of 400 U/L, which is similar to that in other novel pandemics such as the H1N1 pandemic.[12–14] In childhood ALL cases presenting with bone pain, LDH levels > 500 U/L at diagnosis have been reported,[15] similar to what we have seen among our own ALL patients described above (range: 287 to 700 U/L). It is possible that the inflammatory response and increased LDH during the COVID-19 illness, was magnified in our own case with a rapid proliferation of leukemic blast cells[16,17] associated with a very short duration of symptoms.

There was no clinical evidence of leukemia in our patient when he was hospitalized initially with COVID-19 as he had a normal CBC without the presence of atypical lymphocytes or lymphoblasts on the peripheral smear, lacked splenomegaly and presented with typical symptoms of COVID-19 without complaints of bone pain which only arose after he was discharged home. Patients do not develop clinical symptoms of COVID-19 for up to 2 weeks (and sometimes longer) following their initial exposure to a contagious individual. Hence, in our own patient, there may have been an approximate window of at least 3 to 4 weeks from his first COVID-19 exposure (acting as the "second hit") until the clinical diagnosis of ALL.

Activation-induced cytidine deaminase (AID) expression is increased in preleukemic B-cell precursor cells, with AID promoting secondary genetic changes that may lead to subsequent leukemia development.[5] Kaneko et al[18] reported that patients with COVID-19 lost expression of Bcl-6+ germinal center B cells, maintained preservation of AID+B cells; and had a block in Bcl-6+ T follicular helper cell (T_{FH}).[18] Theoretically, this T_{FH} block may lead to a loss in regulation of B-cell maturation, leading to the production of dysregulated B cells, which could be a mechanism linked to infection-associated leukemogenesis.

Following the SARS CoV pandemic in 2013, Hong Kong implemented a public health campaign to curtail the spread of the virus entailing multiple measures including school closures and promoting of wearing face masks. A brief reduction in the incidence of common infectious diseases as well as childhood leukemia was observed during this campaign which lasted 2 months. It was postulated that this decreased incidence may have been due decreased infectious exposure.[19] In the southern hemisphere including Australia (whose fall and winter seasons are opposite to the northern hemisphere), there have been a decrease in the number of cases of respiratory syncytial virus and influenza which are typical for the fall and winter months.[20] With the physical restrictions implemented during initial stages of the COVID-19 pandemic in the United States, a marked decrease in common pediatric infectious diseases has also been reported,[21] though it is too early to determine how this may ultimately impact the incidence of new ALL cases.

In the United States, most public schools have been physically closed since mid-March 2020 and education transitioned to virtual online teaching. As the pandemic continues to spread without abatement, the United States is grappling with issues related to reopening major parts of society and in particular, opening schools with in-person teaching as opposed to virtual learning. Will the onset of the fall 2020, lead to a major spike in the number of pediatric COVID-19 infections with more frequent physical interaction between children and will this lead to an increase in childhood ALL cases, with COVID-19 being the "second" leukemogenic hit? Real-time tracking of the number of ALL cases diagnosed in the near future, will potentially answer this question.

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