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Case Series

Acute lymphoblastic leukemia after COVID-19 infection: a coincidence or a second hit

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ABSTRACT

Since the advent of COVID-19 in 2019, the virus has affected all age groups and has a very wide clinical spectrum, ranging from asymptomatic infection to serious life-threatening complications including multi-organ dysfunction syndrome in children. The virus tends to affect all organ systems including the hematological system. There are many contradictory views on the effect of the COVID-19 pandemic on the incidence of hematological malignancies. Some studies have shown an increased incidence of acute lymphoblastic leukemia (ALL) after COVID-19 infection supporting the Greaves two-hit hypothesis of leukemogenesis, while others have shown a decline in the incidence of ALL postulated to be due to widespread lockdown and decreased exposure to environmental pathogens. We report the cases of three children who were diagnosed with acute lymphoblastic leukemia shortly after the initial diagnosis of multisystem inflammatory syndrome in children (MIS-C) or COVID related transient erythroblastopenia of childhood.

Keywords: COVID-19, MIS-C, ALL, Hematology, Oncology, Leukemogenesis, Pathogenesis, Incidence, Pediatrics

INTRODUCTION

Since its advent in late 2019, COVID-19 has become a global pandemic affecting more than 90 million people worldwide with deaths crossing 10 million worldwide as of July 2022.[1] The clinical spectrum of COVID-19 ranges from asymptomatic or mild infection to serious life-threatening complications including multi-organ dysfunction syndrome (MIS-C). Our understanding of the virus and its clinical manifestations in children is evolving as we are uncovering rare presentations and complications. Additionally, our understanding of the hematological manifestations of COVID-19 is mainly derived from adult studies, due to the lack of large multi-center studies; our knowledge is based mainly on single-institution experiences and case reports. There are many contradictory views on the effect of the COVID-19 pandemic on the incidence of acute lymphoblastic leukemia (ALL) in children. There are some studies which show a decline in the incidence of ALL since the pandemic which has been attributed to widespread lockdown leading to decrease in exposure to pathogens and other environmental factors which play a role in leukemogenesis.[2] Other studies and case reports however favor Greaves two hit hypothesis and postulate that COVID-19 infection acts as a second hit responsible for leukemogenesis in genetically predisposed children.[3-7] We present a case report of children who were initially diagnosed with MIS-C or COVID related transient bone marrow suppression and later found to have B cell ALL.

CASE SERIES

Case 1

A 6-year-old Caucasian female with a significant medical history of recurrent urinary tract infection presented to a free-standing emergency department (ED) with fever, decreased appetite and activity; and was found to have pancytopenia. On examination, she was febrile, with pallor and ecchymosis over both shins. The rest of the exam was unremarkable. Laboratory work showed leukopenia (white blood cells (WBC) count, 1500/cu.mm with absolute neutrophil count (ANC) of 270/cu.mm and absolute lymphocyte count (ALC) of 1200/cu.mm), anemia (Hb level, 3.8 g/dl), and thrombocytopenia (platelet count, 78000/cu.mm). Peripheral smear review showed normocytic, normochromic anemia, neutropenia, lymphocytopenia, and no nucleated red blood cells (RBCs) or blasts. The reticulocyte count was 3.2% and erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were elevated to 71 mm/hour and 6.79 mg/l respectively. Comprehensive metabolic panel (CMP), including uric acid, was normal, urinalysis was negative, and ferritin level was slightly elevated to 425 ng/ml. Coagulation profile, including D-dimer and fibrinogen levels, were normal. The respiratory viral panel was positive for rhinovirus/enterovirus and COVID-19. Chest radiography showed infiltrates in the lung fields suspicious for COVID pneumonia. She was admitted to our inpatient unit and received a total of 15 ml/kg packed red blood cell (PRBC) and started empirically on cefepime. Due to the suspicion of leukemia, flow cytometry was also performed on peripheral blood which was normal. She did not meet the criteria for MIS-C; therefore, she was presumed to have bone marrow suppression from COVID. Her clinical condition improved within a few days after admission, and she was discharged home. On follow-up with pediatric oncology, she continued to have pancytopenia a month after discharge; therefore, a bone marrow aspiration and biopsy was performed. She was found to have B-cell ALL (Figure 1a). She was started on a high-risk ALL protocol owing to unfavorable cytogenetics (iAMP 21 and subclonal MYC rearrangement) and is currently in remission.

Case 2

A 2-year-old healthy African American female presented to a free-standing ER with a history of fever, lethargy, loss of appetite, cough, and congestion for a month. She had a history of exposure to COVID-19 as her immediate family members had COVID-19 infection a month prior to presentation. On work-up at an outside ED, she was found to have anemia and severe neutropenia, along with elevated inflammatory markers; therefore, she was referred to our hospital for further evaluation and management. On presentation to our ED, she was febrile, tachycardic, and tachypneic on exam. She had signs of respiratory distress in the form of subcostal retractions, and crackles were heard bilaterally on auscultation. The rest of the examination was unremarkable. Laboratory work showed leukopenia (WBC count, 1300/cu.mm with an ANC of 0/cu.mm, and an ALC of 1300/cu.mm), normal Hb level of 13.5g/dl and thrombocytopenia (platelet count of 117,000/cu.mm) and reticulocyte count of 0.1%. A CMP, uric acid and LDH, were normal. ESR was elevated to 129 mm/hour, CRP elevated to 14.52 mg/l, coagulation profile showed slightly elevated D-dimer of 0.88 mcg/ml, and fibrinogen elevated at 740 mg/dl. The respiratory viral panel was negative, but the COVID IgG was positive. Chest radiography showed left lung opacity suggestive of pneumonia, EKG and transthoracic echocardiogram were normal. The patient was started empirically on cefepime. She met the criteria for MIS-C; therefore, she was treated with IVIG and aspirin with a contingency to start steroids if she did not respond. Her peripheral smear, however, showed some abnormal looking cells suspicious for blasts; therefore, flow cytometry was sent from peripheral blood, and steroids were held. Flow cytometry showed 9% B lymphoblasts; therefore, she was scheduled for bone marrow aspiration and biopsy which showed B-cell ALL (Figure 1b). She was started on a SR ALL protocol owing to favorable cytogenetics (hyperdiploidy, trisomy 4, 9, 10, 17, 4 copies of IGH, tetrasomy 21, 3 copies of PBX1, and MYC). She is currently in the maintenance phase of chemotherapy and is doing well.

Case 3

A 18 month old healthy Hispanic female presented to a free-standing ED with history of loss of appetite, and lethargy for 2 weeks prior to presentation. Laboratory work from an outside ED was significant for severe anemia, reticulocytopenia and acute COVID-19 infection. The patient was referred to our hospital for further evaluation and management. Laboratory tests revealed anemia (Hb level, 4.9 g/dl), a normal WBC count of 7000/cu.mm, an ANC of 1020/cu.mm, with a normal ALC (5600/cu.mm), and platelet count (181,000/cu.mm). The reticulocyte count was 0.1% and the peripheral smear showed normocytic, normochromic anemia with reactive lymphocytes, a few hematogones, and a few large platelets, but no blasts were noted. CMP, uric acid and LDH were normal. The coagulation profile was normal except for a slightly elevated d-dimer of 1.2 mcg/ml, iron studies were normal. CRP was elevated at 4.6 mg/l and hemoglobin electrophoresis was normal. Flow cytometry was sent from peripheral blood due to the suspicion of leukemia, which was normal. She was transfused with a total of 15 ml/kg of packed red cells and discharged home in a clinically stable condition with a diagnosis of transient erythroblastopenia of childhood from acute COVID-19 infection. On follow-up in the pediatric oncology clinic a week later, she was found to have 25% blasts in the peripheral smear. Bone marrow aspiration and biopsy was done which confirmed the diagnosis of B-cell ALL (Figure 1c). Due to insufficient sample, cytogenetics could not be done on the bone marrow sample. She was started on a SR ALL protocol and is currently in remission and doing well.

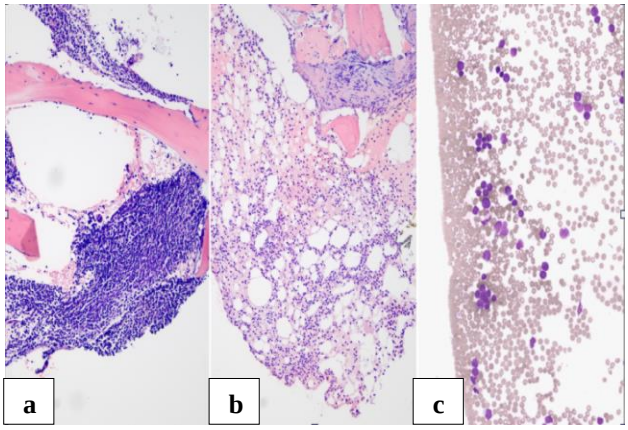

Figure 1: Images from the three patients reported herein (a) bone marrow core biopsy is hypercellular and shows near total marrow effacement by a uniform population of immature B-lymphoblasts (hematoxylin and eosin, 100x), (b) bone marrow core biopsy shows moderate cellularity and partial effacement by a population of monotonous B-lymphoblasts (hematoxylin and eosin, 100X), and (c) bone marrow aspirate showing a uniform B-lymphoblast population representing the majority of marrow progenitors (Wright-Giemsa, 400x).

DISCUSSION

Leukemia is the most common cancer diagnosed in children and adolescents younger than 20 years of age and accounts for 25.1 percent of all cancer cases in this age group. From 2013 to 2017, the most recent five years for which data are available, leukemia and lymphoma accounted for 39 percent of all cancer types in children and adolescents younger than 20 years. Leukemia is the second leading cause of cancer deaths and accounts for 26.1 percent of all cancer-related deaths among this age-group.[8] The most popular theory of leukemogenesis was first proposed by Greaves in 1988.[9] The 'two hit' hypothesis described by Greaves suggest that ALL arises from two separate events, the first event is a mutation in-utero leading to fusion gene formation or hyperdiploidy which generates a pre-leukemic clone. The second hit or event usually occurs when an environmental factor or infection triggers secondary epigenetic changes or genetic alterations necessary for the final step of leukemogenesis or causes immune dysbalance which creates a permissive environment for immune evasion of pre-leukemic clones.[5] This delayed infection model is based on the evolutionary theory that immune cells were programmed to prevent infections in infancy and exposure to these infections is necessary for development of a functional adaptive immune system in adulthood.[3] One example of this hypothesis is ETV6-RUNX1 + ALL, which comprises 25% of B cell ALL cases. It is shown that 5% of all healthy newborns carry the first hit, of which 0.2% later develop B cell ALL.[10] In context of the delayed infection model, it will be interesting to study COVID-19 and the potential role it plays as a second hit in the leukemogenesis. There appears to be emerging evidence in favor of this theory as we are seeing more cases of ALL unravelling after infection with COVID-19. Our cases also seem to support this theory.

However, large multicenter studies are needed to further explore the potential molecular pathogenesis of ALL and hematological malignancies in children with a history of clinical or subclinical infection with COVID-19 virus.

CONCLUSION

In conclusion, in patients with persistent pancytopenia in the context of recent infection or exposure to COVID-19, oncological etiology must still be considered, and close patient follow-up must be ensured.

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