B cell acute lymphoblastic leukemia following mild COVID-19 in an 11-year-old boy

Hui Chen[1], Qian Xu[2], Yi Liu[3], Wenyu Gong[3], Jun Li[4], Jing Liang[3], Xue Zhang[3], Runhui Wu[1], and Zhenping Chen[3]

[1]Beijing Children's Hospital
[2]Chengdu Women's and Children's Central Hospital
[3]Beijing Children's Hospital Capital Medical University
[4]Beijing Key Laboratory of Pediatric Hematology Oncology, National Discipline of Pediatrics, Ministry of Education, MOE Key Laboratory of Major Diseases in Children; Hematology Oncology Center, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health

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Abstract

Coronavirus disease-2019 (COVID-19) has infected millions of people with high lethality in the world, but little is known whether severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has impacts on triggering pediatric acute lymphoblastic leukemia (ALL). We present a case of a child with atypical clinical manifestation who developed B-cell acute lymphoblastic leukemia following a mild symptomatic COVID-19 infection. This case underlines the risks of potential oncogenic effects with the history of this viral infection and a state of immunosuppression.

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Hui Chen[1]*, Qian Xu[2]*, Yi Liu[1], Wenyu Gong[1], Jun Li[1], Jing Liang[1], Xue Zhang[1], Zhenping Chen[1#], Runhui Wu[3#]

1. Hematologic Disease Laboratory, Hematology Center, Beijing Key Laboratory of Pediatric Hematology Oncology; National Key Discipline of Pediatrics (Capital Medical University); Key Laboratory of Major Diseases in Children, Ministry of Education; Beijing Pediatric Research Institute, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, China, 100045
2. Department of Hematology & Oncology, Chengdu Women's and Children's Central Hospital, School of Medicine, University of Electronic Science and Technology of China, China, 611731
3. Hematology Center, Beijing Key Laboratory of Pediatric Hematology Oncology; National Key Discipline of Pediatrics (Capital Medical University); Key Laboratory of Major Diseases in Children, Ministry of Education; Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, China, 100045

*Hui Chen and Qian Xu contributed equally to this work.

#Correspondences:

Runhui Wu,

Capital Medical University, National Center for Children's Health,

56 Nanlishi Rd, Beijing 100045, China; e-mail: runhuiwu@hotmail.com

Zhenping Chen,

Capital Medical University, National Center for Children's Health

56 Nanlishi Rd, Beijing 100045, China; e-mail: zhenpingchen@outlook.com

Abbreviations

COVID-19 Coronavirus disease-2019

SARS-CoV-2 severe acute respiratory syndrome coronavirus 2

ALL B cell acute lymphoblastic leukemia PCR Polymerase Chain Reaction RNA Ribonucleic Acid CBC complete blood count Treg regulatory T cell DNT double-negative T cell TFH T follicular helper cells EBV Epstein-Barr virus

Abstract

Coronavirus disease-2019 (COVID-19) has infected millions of people with high lethality in the world, but little is known whether severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has impacts on triggering pediatric acute lymphoblastic leukemia (ALL). We present a case of a child with atypical clinical manifestation who developed B-cell acute lymphoblastic leukemia following a mild symptomatic COVID-19 infection. This case underlines the risks of potential oncogenic effects with the history of this viral infection and a state of immunosuppression.

Keywords: COVID-19, SARS-CoV-2, acute lymphoblastic leukemia, pediatric

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) classified by the World Health Organization in March 2020 [1], has become an outbreak around the world. However, compared to adults, the coronavirus disease 2019 (COVID-19) may less impact the pediatric population with most having a milder symptoms [2]. In general, COVID-19 in children very less than adults, haematological disease following SARS-CoV-2 infection in pediatric patients is rare. Here, we reported a pediatric case who developed B cell acute lymphoblastic leukemia (B-ALL) following mild SARS-CoV-2 infection. A Chinese family was diagnosed as mild type of COVID-19 infection in Belarus. Without any treatment, SARS-CoV-2 RNA and COVID-19-specific antibodies IgM were negative after two weeks. But the boy in this family showed bone pain and pancytopenia after nineteen days from diagnosed COVID-19. With basic supportive treatment, his symptoms and hemograms returned to normal. Previous symptoms appeared again with significantly elevated white blood cells. As well, blast cells also experienced transient decline and increased again without any treatment. For further diagnosis and treatment, they were back to China. Eventually laboratory findings confirmed B-ALL in Beijing Children's hospital.

Case description

An 11-year-old Chinese boy was presented with fatigue and anosmia for three days in Belarus, whose SARS-CoV-2 of nasopharyngeal and oropharyngeal swabs were positive on December 27, 2020. Therefore, he was diagnosed as mild type of COVID-19 infection, as well as his parents. Without any treatment, the symptoms disappeared three days later. SARS-CoV-2 RNA and COVID-19-specific antibodies IgM were negative after two weeks. About sixty days later from confirmed COVID-19, COVID-19-specific antibodies IgG also turned negative. Since then, SARS-CoV-2 RNA and COVID-19-specific antibodies IgM and IgG were negative by consecutive nasopharyngeal PCR.

About nineteen days later from diagnosed COVID-19, he showed transient pain in his left thigh and waist, however the symptoms disappeared without any treatment. Then he had a fever (38.0-38.6) accompanied by chest pain occurred, no cough and short-breath after twenty-nine days confirmed COVID-19. Chest X-ray examination was finished in local hospital of Belarus and showed acute bronchitis. His symptoms relieved

with five-day antibiotics treatment. Then he was hospitalized in a local hospital soon, because his complete blood count (CBC) test showed cytopenia (Table S1) and immature cells found in peripheral blood smear, Ultrasound examination of abdomen revealed hepatosplenomegaly, and anti-bacterial treatment was ineffective. About forty days later from diagnosed COVID-19, he was transferred to another hospital of Belarus for further treatment. The bone marrow aspirations at two sites were performed and the procedure indicated immature cells were 18.75% and 10% respectively. The bone marrow biopsy indicated lymphocytes proliferation and blasts cells increased. However, the percentage of immature cells in bone marrow didn't meet the diagnostic criteria for ALL, the doctor recommended close follow-up. Then the boy didn't receive any treatment and returned to China for further diagnosis and treatment. The CBC test showed his hemoglobin and platelets value gradually increased to normal during the isolation of COVID-19 (Table S1).

After the end of COVID-19 isolation period, he came to Beijing children's hospital on March 23 without any symptoms. Physical examination revealed a good general condition and no hepatosplenomegaly. Laboratory findings showed CBC test was at normal level (Table S1). There was 10% blast cells in bone marrow aspirate smears. However, blast cells on peripheral blood smear and flow cytometry (Fig.2A) were not present on March 23. Cytogenetic analyses revealed normal karyotypes. Common fusion genes, such as TEL/AML1, BCR/ABL, E2A/PBX1, MLL/AF4, SIL-TAL1, were negative. One week later, lymphoblasts was identified about 4% in bone marrow by flow cytometry. He was considered to be a reactive blast cells proliferation caused by the SARS-CoV-2 infection and continued to observe without any treatment. Until April 16, the patient was admitted to our hospital with persistent left thigh pain and fever for five days. The CBC test revealed an elevation of white blood cell count and absolute neutrophil count with circulating blasts were present (Fig.1J). Also a significant elevation of C-reactive protein (up to 101.6mg/L) was found. Lymphoblasts were 50% in bone marrow smear. Lymphoblast B cells expressing $CD45^{dim}$, TdT, CD19, and $CD10^{bri}$ were found in peripheral blood by flow cytometry (Fig.2B-D). As well, we reviewed HE staining bone marrow biopsy which finished in Belarus, immunohistochemistry was performed to identify the blast cells, which was identified B lymphoblast cell expressing CD34 , TdT , CD10 and CD20 (Fig.1A-F). The patient was diagnosed B-ALL. His family decided to return to the local hospital for chemotherapy. In addition, significant immune dysregulation was observed with higher proportion of regulatory T cells (Treg), double-negative T cells (DNT) and T follicular helper cells (TFH) (Figure.S1).

Discussion

Many studies demonstrated that majority of symptomatic cases in children were described as mild and children were less likely to develop severe illness than adults [3]. Several reports suggested that patients with cancer might be at increased risk of developing COVID-19 [4]. However, the knowledge of relationship between children with cancer and COVID is still limited. In this study, we reported a boy developed B-ALL with recent SARS-CoV-2 infection. His atypical clinical manifestation was different from B-ALL. We speculated the proliferation of lymphoblasts might be caused by SARS-CoV-2 infection temporarily until laboratory findings confirmed B-ALL.

Does SARS-CoV-2 infection have an impact on the development of childhood ALL? Due to lack of literature, there are sporadic reports about COVID-19 concurrent in newly diagnosed ALL [5,6] or during maintenance therapy [7], or reactivation with pre-existing ALL [8] in children. Different from above, our case is one of the few cases developed ALL following SARS-CoV-2 infection so far as we know [9,10]. Leclercq et al reported an 8-year-old Caucasian boy with an extensive maculopapular rash and pancytopenia with recent SARS-CoV-2 and EBV infections and early stage B-ALL [9].

SARS-CoV-2 infections might be related to the immune response including cellular and humoral immune [11,12]. In our report, significant higher proportion of Treg, DNT and TFH cells was observed, which indicated immune dysregulation might play a role in this patient. It was widely spread a hypothesis that ALL arised by "two-hits" [13,14]. The "first-hit" occurred prenatally with a leukemia- associated genetic change. A subsequent "second-hit" occurring postnatally in a population of preleukemia clone would lead to the proliferation of leukemia cells. So-called "second-hit", is postulated to be exposure to a common infectious agent (eg, virus) in a susceptible child who was under an abnormal or over- stimulated immune response. In

the present study, given the child case who developed B-cell ALL following a SARS-CoV-2 infection, with immune abnormalities, we make a scientific hypothesis: the potential possibility of infection with SARS-CoV-2, could exacerbate the patient's immuno-compromised state and induce an immune response that could allow pre-leukemia cell clone proliferate to facilitate the development of pediatric ALL. It is possible that the infection of predisposed children by COVID-19 act as a "second-hit", leading to a driving force of developing ALL.

In conclusion, we reported a rare child case who developed B-cell ALL following a SARS-CoV-2 infection. Whether COVID-19 infection being the "second" leukemogenic hit in childhood ALL, need to answer in the future. Further studies are needed to enlarge the case number to explore the potential oncogenic effects of SARS-CoV-2 in children.

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Figure Legend

Figure 1. Bone marrow core biopsy specimen(A-F). Sheets of immature blasts on H&E stains (A, ×200; B, ×400), with a subset positive for CD34 (C, ×200), TdT (D, ×200), CD10 (E, ×200), CD20(F, ×200).

Bone marrow and peripheral blood smears (G-J). Bone marrow aspirations showed sheets of small- to intermediate-sized blasts with high nucleus to cytoplasmic ratio and dispersed nuclear chromatin on March 30,2021(G) and April 16,2021(H). Peripheral blood smears showed atypical lymphoid cells with immature-appearing chromatin on March 30,2021(I) and April 16,2021(J).

Figure 2. Flow cytometry immunophenotyping of the blasts in peripheral blood and bone marrow. No blasts were presented in peripheral blood on March 23(A). Peripheral blood showed CD45 dim cells with TdT, CD123, CD19 and bright CD10 expression on April 16 (B-D). In bone marrow, a characteristic aberrant lymphoblast phenotype with CD34, CD19, CD10, CD22 and CD20(partial) positive on March 30(E-H).

Figure S1. Suppresion T subtypes assays by flow cytometry. On March 30 (A-C) and April 16 (D-F), flow cytometry immunophenotyping in peripheral blood showed a higher proportion of CD3+CD4+CD25+Foxp3+ Treg(A,D), CD3+TCRαβ+CD4-CD8- DNT(B,E) and CD3+CD4+CD185+CD279+ TFH(C,F).