COVID-19, Acute Lymphoblastic Leukemia and Down Syndrome: A Short Review and a Case Report

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Abbreviations	
ALL	Acute lymphoblastic leukemia
DS	Down syndrome
TTCR	Time to clinical recovery
B-ALL	B-cell precursor ALL
CR	Complete remission
EFS	Event-free survival
WBCs	White blood cells

AML	Acute myeloid leukemia
RSV	The Respiratory Syncytial Virus
CNS	Central nervous system
BFM	Berlin Frankfurt Münster
CT	Computed tomography
SpO2	Blood oxygen saturation levels
PCT	Procalcitonin

Contributors' Statement Page

Dr Arafat conceptualized and designed the study, coordinated data collection, drafted the initial manuscript and critically reviewed the manuscript for important intellectual content.
Prof Sadykova conducted the clinical work, coordinated data collection, reviewed and revised the manuscript.
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All authors approved the final manuscript as submitted and agree to be accountable for all aspects
of the work.

Abstract

In late December 2019, Chinese citizens of the city of Wuhan, China, had shown symptoms of viral pneumonia that were not very common, with various presentations with different grades of severity, and poor response to the regular treatment. With tremendous clinical and research work, the causative of the disease outbreak has been identified as COVID-19 and has been recognized as the novel coronavirus (SARS-CoV-2), which later continued to make the headlines when the World Health Organization announced it as a pandemic on March 11, 2020, after it had hit many parts in the globe with worrying rates of morbidity and mortality. Although available data has expressed that moderate or even mild forms of the disease are expected amongst most of the pediatrics cases, very limited data are available on the prognosis and the complications of the disease on the immunocompromised, especially oncology patients. We report a case of relapsed Precursor B-cell acute lymphoblastic leukemia (ALL) of a child with Down syndrome (DS) and COVID-19 and outline the treatment regimen that we used.

Study Highlights

- Severe forms of COVID-19 in children are not unlikely, and CT scans of pediatric patients with COVID-19 could be presented with ground-glass opacities bilaterally.
- Tocilizumab seems to have promising results in severe cases of children with COVID-19, unlike hydroxychloroquine with a macrolide that failed to reduce the time to clinical recovery (TTCR) and did not improve the severity of the disease.
- To the best of our knowledge, this is the first report of a case of combined risks of Down syndrome, high-risk ALL and COVID-19, and its successful management.

Introduction

SARS-CoV-2 is a fierce disease that has been diagnosed in 188 countries and regions with more than 36 million diagnosed cases and has claimed lives of more than one million people worldwide, as of the day of writing this article, October, 8th, 2020.[1]

Early reports from China have shown that children are less susceptible toward being severely affected by COVID-19 [2], and early lockdown approaches that were adopted worldwide as well as early closure of schools and kindergartens could be the reason for less exposure of children to COVID-19. In addition, the probability of children being tested for SARS-CoV-2 is less likely

since they are presented mainly with mild symptoms, and this could be among the reasons that contribute to fewer reports of COVID-19 in children compared to adults. Although many reports have shown that severe cases of COVID-19 can happen in children with even fatalities, most of the reports have expressed that children are most likely to have asymptomatic, mild or moderate forms of the disease or have their symptoms subside and recover within two weeks of the disease onset. At the same time however, children with underlying serious health conditions such as cardiovascular disease, chronic pulmonary disease, and immunosuppression (e.g. related to chemotherapy, radiation, cancer) appear to be at a higher risk of contracting a severe form of COVID-19.[3]

The most common malignancy in adolescents and children alike is acute lymphoblastic leukemia (ALL). Approximately 85% of ALL cases are B-cell precursor ALL (B-ALL). The survival rate in children with early diagnosed ALL has shown wonderful stats over the past sixty years, from 10% back then to 90% recently.[4,5] Studies have shown that as much as 2% of cases are refractory to induction chemotherapy [6], and 10-15% of cases with ALL still show relapse.[7] However, a second complete remission (CR) can be reached in most of the cases, and 55% of them can experience another relapse.[8,9] The event-free survival (EFS) in ALL Children with the first relapse over the past two decades is still poor, at around 35-50%.[9,10] The initial count of the white blood cells (WBCs) and the age of the patient are highly predictive of the outcome, as fewer initial WBCs and younger age cases are most likely to have a better outcome. A consensus approach to classifying the risk and management of children with ALL defined children who are aged 1 to 9.99 years and with initial WBC count of less than 50,000 per cubic millimeter as *Standard Risk*, while children aged ≥10 years, initial WBC count ≥than 50,000 per cubic millimeter, or both are classified as *High Risk*.[11] Infants, older teenagers, DS patients, and those who are on intensive therapy are at high risk of death.

Studies have expressed better outcomes of patients with acute myeloid leukemia (AML) and DS than ALL and DS patients.[12] That is most likely due to resistance of trisomiclymphoblasts to cytotoxic drugs, unlike the better response to cytotoxic drugs of myeloblasts from patients with DS and AML, which accounts for better curable rates.[13] Patients of DS have been showing higher frequencies of altered levels of drug toxicities, or more commonly, mucositis, cardiotoxicity, infections, and myelosuppression.[14]

DS patients are at higher risks of H1N1- and respiratory syncytial virus-related mortalities and higher rates of mortality due to pneumonia and sepsis. However, studies on DS patients and COVID-19 in children are rare, which makes it unclear how severe the outcome in those patients might be. According to The Respiratory Syncytial Virus (RSV) Gold Study, children with DS are highly susceptible to death resulting from RSV.[15] A Mexican team during the H1N1 2009 pandemic showed worrying results of increased morbidity and mortality in DS patients, with 335-fold greater deaths, 8-fold more intubation and 16-fold more of the possibility of hospitalization.[16] High incidence of autoimmune disorders, elevated production of cytokines and the characteristic chronic dysregulation of the immune system in DS patients make them more vulnerable to COVID-19 and RSV infections, with the related cause of mortality always pointing at cytokine release syndrome.[17]

Confirmed COVID-19 in a child with ALL was first reported on in early March, 2020, in Wuhan, China [18], with rapid progression of his pulmonary lesion and with respiratory support as treatment. Children with hematological malignancies are probably more susceptible to infection with SARS-COV-2 due to immunodeficiency.

Here we present a case of SARS-CoV-2 in a child with relapsed ALL and down syndrome and report the clinical findings as well as the successful treatment procedures. To the best of our knowledge, this is the first case report of infection of COVID-19 in ALL children with DS.

Written informed consent was collected from our patient and their caregiver (mother). This case report was approved by Kazan Medical State University and the Republican Children's Clinical Hospital Medical Ethics Committee.

Case Presentation

A six-year-and-six-months-old boy with combined relapse (central nervous system (CNS) and bone marrow) ALL and DS was administered to our department after his mother's second smear tested positive for COVID-19 while he was receiving his relapse treatment within ALL-REZ-BFM-2002 protocol.

History

At the age of three years old he was diagnosed with high risk ALL, as his WBCs count was 56k/ µl. No extramedullary nor CNS involvements were detected. With flow-cytometry results, he was diagnosed with pre B cell ALL. The cytogenetic analysis confirmed trisomy 21 (DS). He was treated with ALL-Berlin Frankfurt Münster (BFM-2000) protocol, and complete remission (CR) was reached when he turned 6 years old. Six months later combined CNS and bone marrow relapse occurred. ALL-REZ-BFM-2002 protocol for relapsed ALL was started, and completion of F1, F2 block treatments was achieved on the 8th of April, 2020.

Present History

Upon admission, he was 20.7 kg, with a heart rate 120 bpm, a blood pressure of 115/66 mm Hg, no detection of clinical complaints nor apparent lymphadenopathy, no catarrhal inflammation of the mucous membranes, no hepatosplenomegaly, and auscultation of both heart and chest revealed no abnormalities. His body temperature was 36.9 °C. Laboratory studies were as follows; hemoglobin: 126 g/L, platelet: 180 K/UL, white blood cell count: 6.01 K/ µl, with 62% neutrophils and 19.5% lymphocytes. C-reactive protein level 0.18 mg/L. Coagulation profile: Fibrinogen 2.9g/L, INR: 0.94%, Thrombin time: 30 sec. His mother did not have any complaints and her laboratory studies were unremarkable.

The boy's case was identified under the code U07.2 according to the WHO (https://www.who.int/classifications/icd/covid19/en/), for clinical or epidemiological diagnosis of COVID-19 where a laboratory confirmation is inconclusive, and according to ICD 10: C91.0 (https://icd.codes/icd10cm/C9100) to specify a diagnosis of ALL that have not achieved remission.

Co-trimoxazole 240 mg orally, 3 times a day, 3 days a week (Fri., Sat., Sun.) was prescribed to the child, with close monitoring of the symptoms, reduction of the chemotherapy by 1/3 if needed to avoid toxicity, and order chest computed tomography (CT) to be performed only when necessary to avoid excessive radiation exposure. Oxygen saturation (SPO2) was 96-99%.

On the 6th day of admission, the patient started to develop a fluctuating fever up to 39° C, and CT was ordered which revealed the following: two extensive areas of increased density with air bronchogram on both lungs, rough pleuropulmonary adhesions in the upper and lower lobes of both lungs, signs of diminished air entry on both lungs, patchy nodular consolidations with

peripheral ground-glass opacities in subpleural areas of the lower lobes of both lungs, and bilateral pneumonia. Figure 1a. Oropharyngeal swab continued to test negative for SARS-CoV-2. At this stage his laboratory studies were as follows: hemoglobin: 117 g/L, platelet: 158 K/UL, white blood cell count: 4.96 K/ µl, with 61% neutrophils and 18% lymphocytes. C-reactive protein level 0.39 mg/L, AST: 34 IU/L, ALT: 26.8 IU/L. Despite CT findings, his SPO2 remained over 95%.

Upon these findings and on the 8th day of admission, the following therapy was prescribed: Hydroxychloroquine (6.5 mg/kg orally twice per day on day 1, followed by 3.25 mg/kg orally twice per day for five days), Azithromycin (300 mg once a day for 5 days), and Meropenem (20 mg/ kg/ dose IV every 8 hours). During the first two days of therapy, the temperature rose to febrile numbers up to 3 times a day. CRP indicators were between 3.15 to 4.54 mg/dL, Procalcitonin (PCT) 0.368 ng / ml. but no modification to the therapy was made.

On the 12th and the 14th days of admission, the oropharyngeal swabs were tested positive for SARS-CoV-2. A second chest CT was ordered on the 19th day of admission which showed an increase in the size of the previously described areas (Figure 1a) and the identification of new areas of increased lung tissue density and consolidation. (Figure 1b).

Upon such findings, we made the following modifications: Meropenem was stopped, Co-trimoxazole started to be given IV, Tocilizumab (IL-6 inhibitor) was prescribed (8 mg/kg IV slowly over one hour, diluted in 100 ml 0.45% NaCl once), daily monitoring for coagulation profile, and Dalteparin was prescribed; 0.1 ml (2500 IU / 0.2 ml) 2 times a day, close monitoring for cytokine release syndrome through monitoring, SPO2, blood pressure, CRP, interleukin-6 (IL-6), ferritin, D-dimer, and lactate dehydrogenase (LDH). Following the prescription of Tocilizumab, dramatic improvements were noticed; laboratory results and the general condition of the patient started to improve, on the 4th and 6th days of prescribing Tocilizumab (24th and 26th of admission, respectively); oropharyngeal swabs tested negative for SARS-CoV-2.

After a follow-up for 6 days after prescribing Tocilizumab, upon examination and before discharge, our patient's temperature was 36.6 ° C, heart rate: 90 bpm, the child was calm, the skin was clear and pink in color, no swelling nor congestion of mucous membranes, chest auscultation revealed equal air entry on both lungs with no wheezes, and normal rhythmic heart sounds. The abdomen was soft with no hepatosplenomegaly. Upon discharge from the hospital,

laboratory results were all within a normal range. Table 1. The boy's mother tested negative for COVID-19 by PCR twice within a 48-hour interval, and both the child and the mother were discharged after being cured successfully on the 26th day of admission.

Treatment and Outcome Timeline

The chronology of treatment, PCR results, CRP, patient's clinical condition since the first day of admission until the day of discharge are shown in Table 2.

Discussion

We report a case of combined CNS and bone marrow relapse of a Precursor B-cell acute lymphoblastic leukemia (ALL) of a child with Down Syndrome (DS) and COVID-19 and outline the treatment regimen that we used.

Although first reports of patients with ALL and COVID-19 showed that only respiratory support was needed to achieve a successful cure[18], it was a huge challenge for our team to deal with this case, since it was presented with all of the possible risks of contracting a severe form of SARS-CoV-2, due to the following reasons: ① It was initially diagnosed as *high risk* ALL[11], ② then the combined CNS and bone marrow relapse, which is known to have a bad prognosis and high mortality rates [9], ③ being a case of DS, with the known bad prognosis of patients with ALL and DS compared to patients with AML and DS[12], and the high incidence of infections and altered drug toxicity profile with DS patients, which have a high incidence of mortality due to pneumonia, and sepsis[14], and RSV[15] ④ COVID-19, which is known to cause severe acute respiratory syndrome, ⑤ the likelihood of developing cytokine release syndrome, which is mainly caused by chronic dysregulation of the immune system, the high incidence of autoimmune disorders, and elevated production of cytokines that are common with DS patients[17], and ⑥ lack of guidelines and scarcity of reports (as of the time of writing this report) on the prognosis and how to deal with patients with immunosuppression (e.g. cancer, chemotherapy), DS and COVID-19.

A recent American study suggests that pediatric cases with cancer may not be susceptible to being severely affected by SARS-CoV-2 compared to other children. They also suggest testing of caregivers of the patients, as 17.6% of the caregivers of the patients tested positive for

COVID-19.[19] This was also the case for our patient when his mother tested positive twice before his COVID-19 testing was positive.

Another study was conducted by an Italian team, which reported five cases of cancer in their pediatric hemato-oncology department, all of whom showed a mild form of SARS-CoV-2 and with each being successfully cured; two of them in the hospital, and three at home.[20]

Here we strengthen the hypothesis that hemato-oncology children and COVID-19 are not likely to develop a severe form of SARS-CoV-2. The explanation for the mild form of COVID-19 in child cancer patients could be due to: ① the possibility of a weaker immune response, which limits the trigger of the inflammatory reaction that is required to cause the damage of the disease, ② the fact that immunocompromised patients are often required to be socially isolated, limiting the chances of them contracting the disease, ③ in general, the role of innate immunity in children might be the reason for milder forms of the disease, ④ in children, compared to adults, the low binding ability and the expression levels of angiotensin-convertingenzyme (ACE)-2 (which are necessary for SARS-CoV-2 to bind and initiate its inflammation process) have most likely played a key role in the explanation of mild forms of the disease in children.[20, 21]

Nevertheless, the possibility of severe cases and even fatalities in children with underlying health conditions cannot be thoroughly ruled out, as we look at lessons we have learned from the previous Middle East Respiratory Syndrome (MERS) epidemics.[22]

Interestingly, the CT results were not truly representative of our patient general condition and the SPO2 saturation (did not fall below 96%), as multiple infiltrations, consolidations and GGO were seen on both lungs. Similar to other reports from Korea and China [23,24], what was different from what was reported was that CT findings that are specific to COVID-19 were limited to a single lung segment, unlike the presentation we had with our patient, which could be due to the underlying health conditions that were present in our case. We limited performing CT scans to two sets with consideration of the potential risks of radiation as was suggested by a recent study.[24]

The severity of SARS-CoV-2 infection in DS children is unknown, with a few reports of a severe form of the disease in adult DS cases and the suggestion of paying close attention to the potential risk of developing cytokine storm in these patients. [25,26]

Reduction of chemotherapy in leukemia patients with DS due to the fear of treatment-related toxicities has been an area of debate, with some reports suggesting a reduction of the dose and others seeing no significant difference in outcome between those with dose reduction and the control group.[27] Careful consideration for the unique presentation of our case and the underlying health conditions led us to recommend a reduction of the dose of chemotherapy by one third, in case of another relapse that required continuation of the chemotherapy, and with consideration for treatment delay of more than seven days, as the incubation period of SARS-COV-2 is between two to seven days.[28] This was recommended by a recent study from China.[28]

Decisions to use antiviral therapy should be tailored to a case-by-case basis, with consideration for the clinical presentation, disease severity, and underlying health conditions. Another area of recent debate was the efficacy of hydroxychloroquine with or without a macrolide in treating COVID-19 patients. A recent study in adults (which is still being peer-reviewed) showed that patients with COVID-19 who were treated with hydroxychloroquine had their time to clinical recovery (TTCR) significantly shortened and pneumonia improved compared to the control group.[29] A large recent study on adults from *The Lancet* examined the efficacy of hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19 on 14888 patients compared to a control group of 81144 patients, which found no benefit for either hydroxychloroquine or chloroquine alone or with a macrolide in treating COVID-19. Moreover, patients in the treatment group were associated with increased in-hospital deaths and ventricular arrhythmias. The study stirred up a lot of controversy and was recently retracted.[30] Reports of the efficacy of hydroxychloroquine with or without a macrolide in children are now lacking. Our patient who was initially treated with hydroxychloroquine and azithromycin did not show improvement and the TTCR did not show any significant outcome, with his PCR being elevated and his CT findings worsening. It wasn't until Tocilizumab was prescribed that dramatic improvement was noticed, and a successful recovery was achieved on the fourth day of prescription and confirmed on the sixth day of administration, with his second oropharyngeal swab testing negative for COVID-19 by PCR.

Promising results of the efficacy of the IL-6 inhibitor tocilizumab in the treatment of COVID-19 have been reported. A recent study on adults showed that in severe COVID-19 cases, Tocilizumab resulted in a quick decline in inflammatory markers and a reduction of the

requirements for ventilation support.[31] An Italian study on adults with COVID-19 demonstrated positive results when tocilizumab was used in the early stages of the disease in terms of better survival rates compared to the control group.[32] A study of 100 adults with severe COVID-19 revealed significantly positive results with overall clinical improvement and clearance of diffuse bilateral opacities on chest x-ray in 61% of the cases.[33] Although there has been no dedicated study to investigate the efficacy of tocilizumab in treating pediatrics cases of COVID-19, the promising results of these recent studies on adults brings hope for patients with severe COVID-19, but the cost of the drug remains an obstacle to having it widely used, and more clinical trials are required to prove its clinical efficacy.

Conclusion

Being hit with an ambiguous disease (COVID-19) early in January, 2020 created a situation in which a clear and straightforward approach toward management and therapy was severely lacking. With the disease having a high incidence of morbidity and mortality, and its pattern of affecting multibody systems as well as the respiratory system and its association with different syndromes in children, the conditions were and still are a great challenge to work with. Through the relentless efforts of research and clinical trials, promising results and a clearer image of the disease started to unravel, although continuous efforts are still needed and more clinical trials are required to attest to the efficacy of the management regime and the disease pattern of COVID-19 that we know today.

ALL children with COVID-19 tend to have a good prognosis and a mild form of the disease, although children with underlying health conditions might be presented with severe forms of the disease. CT in children should be performed in suspected cases since many pediatric cases have severe abnormalities in their CT scans while their clinical conditions do not represent the underlying pathology of their chest, and bilateral ground-glass opacities are not unlikely to happen in children. We recommend the use of tocilizumab in severe cases of COVID-19 in children, especially for children in the high-risk group.

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Figures legends

Figure 1. Chest CT Scans of Our Patient.

Figure 1 A. Chest CT performed on the sixth day of admission shows patchy nodular consolidations with peripheral ground-glass opacities in subpleural areas of the lower lobes of both lungs and bilateral pneumonia. B. The second chest CT which was performed a few days after the first one shows the worsening of the condition with an increase in the size of the previously described areas (figure 1a) and the identification of new areas of increased lung tissue density and consolidation.

Table 1. Laboratory results upon discharge from the hospital:

IgG	C3	C4	IgA	WBC	Segs	Ly	HGB	PLT	Fibrinogen	PTI	INR	AST	ALT	Urea	Creatinine	CRP
6.86 g/L	118 mg/dL	39 mg/dL	0.6 g/L	6,22 k	51%	27%	118 g/L	243 k/µL	2.2 g/l	56.6%	1.37	37 IU/L	28 IU/L	3.5 Mmol/L	37 µmol/L	0.35 mg/L

k= thousand, Segs= segmented neutrophils, Ly= Lymphocytes, HGB= Hemoglobin, PLT= Platelets, PTI= Prothrombin index, INR=international normalized ratio, AST= Aspartate transaminase, ALT= Alanine transaminase, CRP=C-reactive protein

Table 2. Treatment and Outcome Timeline:

Day of admission	Treatment			CRP (mg/L)	PCR results for COVID-19	Clinical condition
	Hydroxychloroquine and Azithromycin	Meropenem	Tocilizumab			
1st- 7th				Irrelevant	-ve	Stable
8th- 13th	From 8th till 12th	Started on 8th		↑0.18- 0.56	+ve on 12th	Fever, consolidations, GGO in CT
14th- 19th		Till 18th		↑↑2.31- 4.8	+ve on 14th	Fever, ↑ consolidations, GGO in CT
20th-26th			Single dose on 20th	↓↓4- 0.35	-ve on 24th and 26th	Stable, clear chest on auscultation

CRP= C-reactive protein, PCR= polymerase chain reaction, -ve= negative, +ve=positive, GGO= ground-glass opacities, CT= computed tomography.