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The severity of COVID-19 infection in children with leukemia

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ABSTRACT

Aims: The coronavirus disease 2019 (COVID-19) has been the cause of a global health crisis since the end of 2019. The aim of this study was to evaluate the clinical findings and treatment results of COVID-19 disease in pediatric patients with leukemia.

Methods: All the children and adolescents with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive real-time polymerase chain reaction (PCR) and the presence of underlying leukemia were included in the study.

Results: A total of 44 leukemia patients with COVID-19 infection were included in the study. Their primary diseases were as follows: 36 patients were newly diagnosed with acute lymphoblastic leukemia (ALL), four patients were relapsed ALL, two patients were refractory ALL, and two patients were acute myeloblastic leukemia. The mean age of patients was 104± 62 months. COVID-19 was asymptomatic in 11.4% of patients, mild in 84%, and moderate in 4.5% whereas none of our patients had a severe infection. No severe complications and/or death were observed in our study group.

Conclusion: It has been found that the clinical course of COVID-19 is mild in children and adolescents with leukemia and undergoing chemotherapy or immunosuppressive therapy.

Keywords: Children, COVID-19, leukemia

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing coronavirus disease 2019 (COVID-19) has rapidly evolved from an epidemic outbreak in Wuhan, China.[1] As there were more than 2 million cases of COVID-19 worldwide, the World Health Organization declared COVID-19 a pandemic in March 11, 2020.[2] The SARS-CoV-2 viruses are positive single-stranded RNA viruses and primarily manifested as a respiratory tract infection. It may be cause systemic disease including cardiovascular, respiratory, gastrointestinal, neurologic, hematopoietic and immune system.[3] COVID-19 affects all age groups; however, the pediatric population accounts for only 3%-5% of total cases.[4] In children, most cases of COVID-19 are asymptomatic, and studies have revealed that children have less severe symptoms compared to adults.[5] However, some patients develop life-threatening complications such as acute respiratory distress syndrome, thrombosis, and multiorgan failure.[6]

Children with malignancy are frequently immunocompromised due to both disease itself and chemotherapy they receive which put them at high risk for severe infections, the major cause of mortality. Although data on pediatric cancer patients are limited, the mortality rate in pediatric cancer patients with COVID-19 is extremely low.[7]

This study, which was designed as a single-center retrospective observational study, was aimed to evaluate the clinical findings and treatment results of COVID-19 disease in pediatric patients with leukemia.

METHODS

The study was carried out with the permission of the Ankara City Hospital No:2 Clinical Researches Ethics Committee (Date: 18.01.2023, Decision No: E2-22-3196). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. An informed written consent form was not obtained due to the retrospective nature of the study.

A single-center retrospective study was conducted in our hospital. All the children and adolescents (aged 0-18 years) attending pediatric hematology with a diagnosis of leukemia with confirmed COVID-19

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from nasopharyngeal swab between March 2020 to March 2022 were included. Clinical data, demographic characteristics, and laboratory-imaging findings were retrieved from electronic medical files. COVID-19 diagnosis was obtained with real-time reverse transcription polymerase chain reaction (RT-PCR) assay (nasopharyngeal swab) for SARS-CoV-2. As our clinic policy nasopharyngeal RT-PCR test was performed in all patients and caregivers with symptoms of respiratory infection or asymptomatic patients and caregivers before hospitalization. Follow-up RT-PCR test data were collected if available. If a patient had RT-PCR positivity after a negative report with minimum 14-days period was accepted re-infection. RT-PCR tests were performed in the Microbiology Department of our hospital. Turnaround time for the COVID-19 RT-PCR test result was 6-12 hours. Data were recorded from the patient files regarding age, sex, type of leukemia, phase of treatment, symptoms, severity of COVID-19, need for hospitalization, treatment interruptions, hospital course, and outcomes. Severity of COVID-19 are described;[8]

Asymptomatic: Patients with no signs or symptoms of COVID-19.

Mild infection: Patients with mild symptoms including fever, gastrointestinal symptoms, and upper respiratory tract infection symptoms.

Moderate infection: Patients with hypoxia at rest (oxygen saturation < 93%) or presence of pneumonia. Patients with no need for intensive care unit admission.

Severe infection: Patients requiring intensive care unit admission for pneumonia or any of the following: 1. Respiratory rate >30 breaths/min (by age; 3-12 months >40, 1-3 years >30, 3-12 years >25, >12 years >20 breaths/min); 2. PaO_2/FiO_2 < 300; 3. Lung involvement > 50% on imaging within 24-48 h 4. Mechanical ventilation, septic shock, or multiorgan dysfunction.

Febrile neutropenia was defined in individuals with hematological malignancies who showed an absolute neutrophil count of less than 500/mm³ or between 500-1000/mm³ and an expected neutrophil to decrease below 500/mm³ within 24-48 h, and who had a fever as a single temperature of ≥38.3°C or >38.0°C sustained over an hour.[9] COVID-19 recovery was defined by the disappearance of the clinical symptoms in symptomatic patients. The patient was discharged when the clinical symptom improved, and the control RT-PCR result was negative.

Statistical Analysis

Statistical analyses were performed using the SPSS 15.0 statistical package programme. Descriptive statistics of the numerical parametric data were calculated as mean±standard deviation. Categorical variables were described as frequency rates and percentages.

RESULTS

The data of 139 pediatric patients with a diagnosis of acute leukemia who were assessed for SARS-CoV-2 by RT-PCR between March 2020 and March 2022 were evaluated retrospectively. The diagnosis of 117 patients was acute lymphoblastic leukemia (ALL) and 22 was acute myeloblastic leukemia (AML). A total of 44 leukemia patients with COVID-19 infection were included in the study. 36 patients were newly diagnosed ALL, four patients were relapsed ALL, two patients were refractory ALL, two patients were AML. Bone marrow transplantation was done in three of these patients due to high-risk ALL, and these patients had COVID-19 infection while receiving immunosuppressive therapy after transplantation. COVID-19 infection developed during induction, consolidation, or re-induction therapy in 16 of our patients with acute lymphoblastic leukemia and during maintenance therapy in 17 patients. The mean age of patients was 104±62 months; 57% were males, 42% were females. The characteristic features of the patients are described in Table 1.

Table 1. Characteristics and laboratory details of the patients

Patient characteristics	n	%
Age (month)	104±62	
Sex		
Male	25	57
Female	19	43
Underlying diagnosis		
Pre-B ALL	36	83
Relapsed ALL	4	9
Refractory ALL	2	4
AML	2	4
Haemoglobin, g/dL	9.1 (7-11.5)	
White blood cells (/mm³)	1900 (400- 3800)	
Neutrophil count (/mm³)	700 (100-1600)	
Lymphocyte count(/mm³)	980 (550- 1800)	
Platelet count (/mm³)	84000 (11000- 183000)	
CRP (mg/L)	68 (10-195)	

The most common symptoms were fever (n=20, 45.4%), cough (n=15, 34%), sore throat (n=4, 9%), nasal congestion (n=3, 6%), respectively. Mean duration of febrile days was 2.5±2.4 days. The COVID-19 RT-PCR test was positive at the time of initial diagnosis in four patients, and these patients presented with fever. These patients were admitted to our infection service with a diagnosis of ALL and, steroid treatment was started in accordance with the chemotherapy protocol, and intrathecal treatment was performed within the first 3 days. In ALL patients, 6 patients were receiving

induction therapy, 6 were receiving consolidation therapy, 4 were receiving re-induction therapy, 17 were receiving maintenance therapy, 4 were receiving relapsed therapy, 2 were receiving salvage therapy, and 1 patient was in pre-transplantation period and 2 patients were in the post-transplant period. Two patients were receiving AML protocol.

Neutropenia was present in 54.5% of our patient. The mean neutrophil count of our neutropenic patients was 520± 415/mm³. None of the patients had a positive blood or catheter culture. The treatment of patients who received active chemotherapy were interrupted until the SARS-CoV-2 RT-PCR result was negative. The mean days for PCR negativity was 12.3±8.1 days. One of our patients became negative on the 45th day and chemotherapy of this patient was started when the COVID-19 cycle threshold value (the number of cycles that the fluorescent signals undergo to reach the threshold and < 25 values indicate high viral load and >25 indicate low viral load) was 27 on the 39th day of COVID-19 RT-PCR positivity.

According to the disease severity score, 5 patients (11.4%) were asymptomatic, 37 patients (84%) had mild infection, and 2 patients (4.5%) had moderate infection whereas none of our patients had severe infection. One ALL patient receiving maintenance treatment and one with refractory disease developed moderate infection. The patient who was on maintenance therapy, had bilateral air bronchograms and patchy consolidations in her thorax computed tomography, consistent with COVID-19 pneumonia (**Figure 1**) and corticosteroid treatment was given with antibiotics. After 4 weeks of hospitalization, this patient was discharged and continued maintenance therapy. In two patients, COVID-19 RT-PCR positivity was detected again approximately two months after their test became negative and the chemotherapy of these patients were interrupted again.

None of the patients developed multisystem inflammatory syndrome during follow-up. No severe complications and/or death were observed in our study group.

DISCUSSION

In the past two years, it has been clearly demonstrated that critical disease due to COVID-19 is rare in children and the disease progresses milder in children compared with adults.[10] Although few data are available regarding the effect of COVID-19 on pediatric patients with leukemia, the rate of the asymptomatic disease has been reported between 30-80%.[11,12] Among patients with all types of malignancy and COVID-19, children also experience less morbidity and mortality than adults. Only 4-9% of pediatric oncology patients experience a severe or critical COVID-19 course compared to 55% of adult oncology patients.[13,14] Furthermore, the mortality rate of COVID-19-positive pediatric oncology patients was 4%, however mortality rate was 28% in adults with cancer and COVID-19.[15-17]

In this study, 58% of the patients were male, which was consistent with the other studies that reported no significant differences between gender in pediatric patients.[18]

The most common presenting symptom of our patients with COVID-19 were fever as the patients that reported in the most international studies.[19,20] Most pediatric cancer patients with COVID-19 were noted to have a relatively mild illness and it has been claimed that hospitalized cancer patients with COVID-19 were often admitted because of problems with their primary diseases rather than complications of COVID-19 infection.[11,12] Similarly, most of our patients had mild infection, whereas only two patients had moderate infection. Although febrile neutropenia was thought to be a risk factor for a severe COVID-19 infection, we could not observe this in our patients.[21] In the Global COVID-19 in Childhood Cancer Registry, a severe disease frequency was found as 18.4% and death was reported in 3.4% of children with malignancy.[22] In our cohort, none of our patients were followed up in the intensive care unit and no death was observed. Further, none of our patients developed any of the chronic complications of COVID-19, including multisystem inflammatory syndrome in children, after recovering

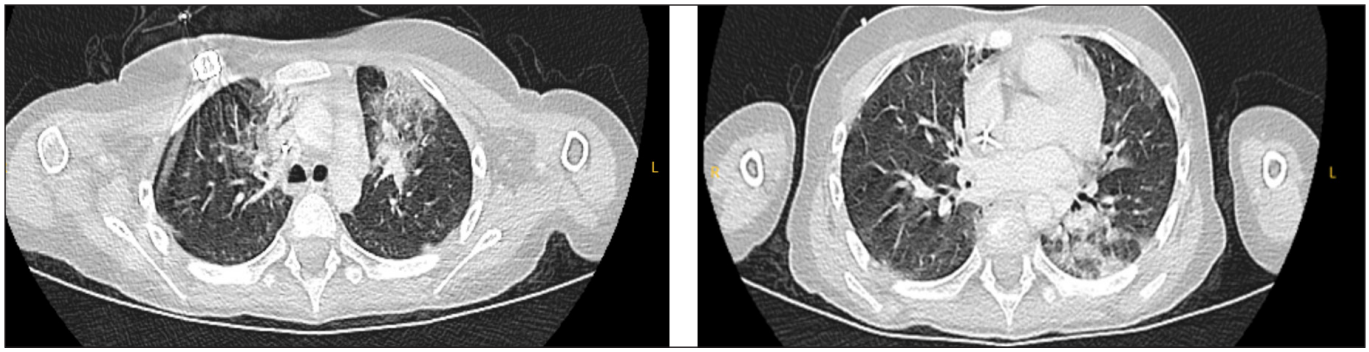

Figure 1a,1b. A computed tomographic scan of the chest showing bilateral air bronchograms and patchy consolidation

from the infection. MIS-C is a heterogeneous manifestations of systemic inflammation and shock and increasingly reported among children and adolescents who already developed antibody against COVID-19.[23] In previous studies, the rates of hospitalization in intensive care, respiratory support and mortality were found to be 63-80%, 33-56% and 0.8-3%, respectively, in healthy children who developed MISC.[24] Our results may be explained by the role of chemotherapy-related immune suppression in the protection against the development of cytokine release storm.[25]

In our study, none of the patients had positive blood cultures. Sepulveda et al.[26] reported that bloodstream infections are very rare in adult and non-malignant patients with COVID-19, like our findings but there are no studies available in pediatric patients.

Chemotherapy was withheld even in asymptomatic patients for all COVID-19 positive patients. So far, no increase in malignancy-related morbidity, relapse or mortality due to this delay of chemotherapy has been noticed.

This study has some limitations. First, it was a retrospective study, and our cohort included a small number of patients. It may be difficult to interpret the data and come to a definite conclusion with a such limited patient group, but all novel information about COVID-19 in special patient groups is valuable for researchers. More prospective studies with larger sample sizes are needed in this subject to elucidate the long-term follow-up results in pediatric patients with leukemia.

CONCLUSION

It has been found that the clinical course of COVID-19 is mild in children and adolescents with leukemia and undergoing chemotherapy or immunosuppressive therapy.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Ankara City Hospital No:2 Clinical Researches Ethics Committee (Date: 18.01.2023, Decision No: E2-22-3196).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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