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ARAŞTIRMA / RESEARCH

Clinical and radiological features of COVID-19 infection in pediatric hematology-oncology and transplant patients

Pediatrik hematoloji-onkoloji ve nakil hastalarında COVID-19 enfeksiyonunun klinik ve radyolojik özellikleri

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Abstract

Purpose: The goal of this study is to explain the characteristics of COVID-19 in this demographic, as well as the impact it had on pediatric cancer care during the pandemic.

Materials and Methods: Fifteen COVID-19 patients diagnosed were studied retrospectively. Clinical, laboratory and radiological data were collected in relation to 15 patients under the age of 18 who tested positive for Sars-CoV-2.

Results: Of the 12117 pediatric hemato-oncological patients tested for COVID-19, 1125 patients showed symptoms, and 14 tested positive. The majority of cases suffered minor illnesses. A total of ten children required inpatient care, five needed oxygen support, and four required mechanical ventilation and later died. It was noted that the duration of real-time polymerase chain reaction (RT-PCR) positivity was prolonged in patients receiving intensive chemotherapy and/or immunosuppressive therapy. Patients' chemotherapy was delayed in all 15 (100%) Sars-CoV-2-positive patients. Although changes visible on chest computed tomography (CT) imaging of children were mainly milder than in adults, radiological findings were more severe in patients who received relatively intensive cancer treatment.

Conclusion: Children who have been treated for cancer or who have undergone a hematopoietic stem cell transplantation (HSCT) may be at greater risk of severe COVID-19 and should be under constant observation.

Keywords:. Chemotherapy, COVID-19, immunocompromised, pediatric, hematology, oncology, Sars-CoV-2

Öz

Amaç: Bu çalışmanın amacı, COVID-19'un bu demografideki özelliklerini, pandemi sırasında pediatrik kanser hastalarının özelliklerini ve malign hastalık tedavisine yaklaşımı ortaya koymaktır.

Gereç ve Yöntem: COVID-19 tanısı alan on beş pediatrik hematoloji onkoloji hastası geriye dönük olarak incelendi. Sars-CoV-2 testi pozitif çıkan 18 yaş altı 15 hastayla ilgili klinik, laboratuvar ve radyolojik veriler toplandı.

Bulgular: Pediyatrik hematoloji onkoloji poliklinik ve servisinde takip edilen, COVID-19 için test edilen 12117 hastadan 1125'i semptomatik olup 14'ü pozitifti. Bir vakaya klinik ve radyolojik özellikleri ile COVID-19 tanısı konuldu. Vakaların çoğunda hafif hastalık bulguları vardı. Toplam on çocuk yatarak tedavi alırken, beş hastaya oksijen desteği gerekti. Üç hastaya mekanik ventilasyon ile solunum desteği gerekti ve sonra kaybedildi. Yoğun kemoterapi ve/veya immünosupresif tedavi alan hastalarda gerçek zamanlı polimeraz zincir reaksiyonu (RT-PCR) pozitiflik süresinin uzadığı görüldü. 15 (%100) Sars-CoV-2 pozitif hastanın tümünde hastaların kemoterapisi ertelendi. Çocukların göğüs bilgisayarlı tomografi (CT) görüntülemelerinde görülen değişiklikler yetişkinlere göre esas olarak daha hafif olmasına rağmen, yoğun kanser tedavisi gören hastalarda radyolojik bulgular nispeten daha şiddetliydi.

Sonuç: Kanser tedavisi görmüş veya kök hücre nakli yapılmış çocuklar ciddi COVID-19 riski altında olabilir ve sürekli izlenmelidir.

Anahtar kelimeler: Kemoterapi, COVID-19, immünsüprese, pediatrik, hematoloji, onkoloji, Sars-CoV-2

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INTRODUCTION

The World Health Organization announced the 2019 coronavirus (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus-2 (Sars-CoV-2) in March 2020[1]. The spread of the disease all over the world in a short time and causing a large number of deaths provoked great panic and anxiety in all parts of society. The disease has been reported in our country as of March 2020. At the time of the study (November 2021), approximately 200 million people have been infected with the virus around the world, and 4 million people have died. In Turkey, more than two and a half million cases have been registered while 50,000 people have lost their lives as a result of Sars-CoV-2[2]. It has been observed that the morbidity and mortality of the infection increase with age, and pediatric cases have accounted for less than 5% of all cases[3]. A limited number of studies on pediatric patients infected with Sars-CoV-2 have been published[3-5]. Based on the literature compiled in this limited period, infected children are generally asymptomatic, and cases involving severe clinical symptoms are less common. However, the clinical picture is more severe in children with underlying diseases such as malignancy, congenital heart disease, or metabolic diseases, or in younger age groups who are receiving cancer chemotherapy or immunosuppressive therapy[4-5]. It is already a widely known fact that the morbidity and mortality of viral respiratory tract infections are higher in this patient group compared to the healthy population[6]. COVID-19 infection, which has very low mortality in children compared to adult Sars-CoV-2 infected patients (0.18% vs 4.3%)[7] has a high mortality rate in patients with comorbidities[8]. There is a lack of guiding information and guidelines for children infected with Sars-CoV-2 who are subject to the immunosuppressive effect of chemotherapy in the treatment of cancers such as leukemia. Studies with a limited number of cases and reports on this subject in the literature have only been able to provide recommendations[9-11]. The fact that RT-PCR test kits are not always helpful in diagnosis due to false-positive results has brought up the importance of radiology[12]. At the time of initial testing, the total positive rate of RT-PCR of throat swabs was reported to be around 57%[13]. Before an RT-PCR assay comes back positive, a chest computed tomography (CT) is an essential tool for early screening and diagnosis of suspected COVID-19 patients[14]. Therefore, chest CT is used in conjunction with clinical status and laboratory tests in the diagnosis and treatment process. The mild clinical course in pediatric patients compared with adult patients highlights the importance of chest CT.

In this retrospective study, we evaluated the clinical, radiological, and laboratory features of our case series of 15 patients infected with Sars-CoV-2, particularly in terms of chest CT imaging of those receiving chemotherapeutic agents and immunosuppressive therapy in a pediatric hemato-oncological and transplantation center as a single-center experience. The purpose of this research is to better understand the characteristics of COVID-19 in this population, as well as the influence it had on pediatric cancer care during the pandemic.

MATERIALS AND METHODS

Sample

From March 11, 2020 to November 30, 2021, a total of 12117 pediatric patients were admitted to Acibadem Adana Hospital pediatric hematology-oncology outpatient clinic and emergency service (The number of patients, excluding repeated applications, was 820). Symptomatic (fever, cough, or fatigue) pediatric patients (n=1125) with a suspected Sars-CoV-2 infection at our hospital pediatric hemato-oncological/transplantation center were evaluated retrospectively. Patients with nonspecific symptoms such as fever, cough, and fatigue who had negative COVID-19 RT-PCR test and patients who were clinically and radiologically incompatible with COVID-19 (n=1110) were excluded from the study (Figure 1).

The study comprised patients who had been diagnosed with COVID-19 infection. The patients were divided into groups I (patient numbers 1 to 11 – undergoing chemotherapy) and II (patient numbers 12 to 15 – undergoing immunosuppressive treatment). There were 11 patients (six with acute lymphoblastic leukemia (ALL); four with acute myeloblastic leukemia (AML); and one with chronic myeloid leukemia (CML)) in group I; and four patients (one bone marrow transplant recipient; two with ALL; one with AML; and one suffering from chronic granulomatous disease) in group II. Where

clinically appropriate, imaging techniques were used in some cases after evaluating the clinical and laboratory results. Where radiological scanning was performed, a posteroanterior (PA) chest X-ray was used initially. Patients who met at least one of the Ministry of Health's imaging requirements (fever ≥ 38 °C, respiratory rate ≥ 22/min, peripheral oxygen saturation (SpO2) ≤ 93% or severe respiratory distress) received a chest CT scan if the aforementioned radiograph was insufficient for diagnosis[15]. All aspects of the study were conducted in accordance with the Helsinki Declaration and were approved by the Clinical Research Ethics Committee of Acibadem University (Decision No: 2021-03-35 and Date: 11.02.2021). Informed consent was obtained from each patient (and their parents) included in the study.

Patient selection

i. Aged between 0 to 18.

ii. Diagnosed with COVID-19 via RT-PCR test.

iii. Receiving/received immunosuppressive cancer or supportive treatment during the study period or within the last 6 months.

Suspected cases were not included without a verified RT-PCR result, which was based on symptoms and/or clinical history. Fifteen patients were diagnosed following a positive RT-PCR test result. One case was diagnosed based on radiological findings despite a negative RT-PCR test result (Figure 1).

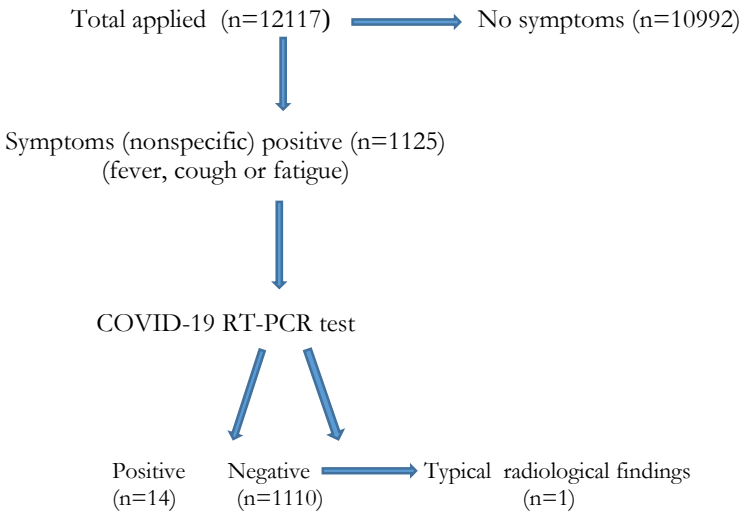

Figure 1. Evaluation scheme of the patients included in the study.

Laboratory parameters

Sars-CoV-2 was detected using a nasopharyngeal swab on all of the patients. In addition, routine COVID-19 tests included a complete blood count, blood biochemistry (blood urea nitrogen (BUN), creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), sodium, potassium, calcium, bilirubin, creatinine kinase (CK), D-dimer, troponin, lactate dehydrogenase (LDH)), prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, ferritin, and C-reactive protein tests.

Imaging techniques

PA chest X-rays were performed using a digital X-ray device with automatic low-dose acquisition features for children.A 64x2 multislice CT device was used to achieve high-resolution low-dose chest CT examinations on all patients. Where children were

able to do so, chest CT examinations were performed while the patients held their breath.

Chest X-ray analysis

Chest X-ray images were evaluated according to the presence of the following findings: I) normal; II) perihilar peribronchial thickening; III) ill-defined nodular opacities; IV) other findings (pleural effusion and lymphadenopathy).

Chest CT analysis

Chest CT images were evaluated according to the presence of the following findings: I) the affected lung side (unilateral–bilateral); b) the affected lung lobe (unilobar/multilobar); c) the affected lung field (peripheral–central); d) the lesion types (crazy paving, ground-glass opacities (GGO), consolidation, pulmonary nodules surrounded by GGO, cavitation, air bronchograms, interseptal thickening, halo sign, inverted halo sign); e) other findings (pleural thickening, pleural effusion, pericardial effusion, pneumothorax, lymphadenopathy).

Treatment

Among the patients with a confirmed diagnosis, those with stable vital signs and normal laboratory and radiological examinations were followed up in the outpatient clinic. Patients with abnormal laboratory parameters or radiological findings typical of COVID-19 pneumonia were treated in isolation on a COVID-19 ward or intensive care unit (ICU).

Hydroxychloroquine monotherapy was applied as the initial course of treatment according to the current guidelines prepared by the Ministry of Health of the Republic of Turkey. Lopinavir/ritonavir, methylprednisolone, and/or convalescent plasma treatment were given to patients whose symptoms did not resolve or who were clinically unstable. Sars-CoV-2 swab samples were tested twice in a row using the real-time reverse transcriptase polymerase chain reaction (RT-PCR) method.

Follow-up

Patients who were recommended for home care were called by phone every day and were asked in detail whether their general condition, newly developing complaints, or current complaints had progressed. They were evaluated twice a week in the COVID-19 outpatient clinic. Their medical histories were taken, physical examinations were performed, and laboratory tests were repeated.

Statistical analysis

Patients' gender, age, hematological and biochemical parameters were evaluated. We used descriptive statistics to analyze patient demographic data. The study groups were compared using a two-tailed Fisher's exact test. Differences between categorical variables were analyzed with the $\chi 2$ test, and numeric variables were compared with the Mann-Whitney U test.

RESULTS

A total of 1125 RT-PCR tests were performed (excluding repeated tests) on patients with clinical findings suggestive of SARS-CoV-2 infection, e.g. fever, cough, and respiratory distress. 15 patients with confirmed SARS-CoV-2 infection among patients who met the inclusion criteria between March 2020 and November 2021 were included in the study. The epidemiological, clinical, and laboratory characteristics of the patients are described in Table 1.

The average age of the patients was 117.5 months. (36-216). Among the patients in our study, nine had ALL (four suffering from a relapse), three had AML (one had suffered a relapse, and one was a post-transplant patient), one had beta-thalassemia major, one was immunodeficient, and one was suffering from sickle cell disease.

With respect to treatment, three patients were receiving ALL IC-BFM 2009, two - AML-BFM 2013, three - ALL-Rez BFM 2002, one - FLAGG-IDA, one - AML IC-BFM 2009 protocol, and four patients were receiving various immunosuppressive treatments, while one patient was taking imatinib.

Only two patients had a history of contact with an infected person. 12 patients presented COVID-19 symptoms. The most common symptoms were fever (91%) and cough (58%). All patients underwent a nasopharyngeal swab examination for Sars-CoV-2 infection via RT-PCR testing, which came back positive in 15 patients (100%).

By the end of the study, 750 tests had been performed in 500 patients hospitalized in our clinic due to different hematological diseases following suspicious clinical findings such as fever, respiratory complaints,

or contact with a Sars-CoV-2 infected individual. However, no Sars-CoV-2 infection was detected.

Laboratory evaluations of the patients at the time of diagnosis are given in Table 1. However, no statistically significant difference was found between complete blood count, coagulation parameters, D-dimer, plasma ferritin, CK, LDH, troponin, and CRP values ($p>0.05$). Chest X-ray images were obtained in all patients, but twelve of them (80%) were also evaluated on the basis of chest CT scans (Table 2).

Eight of fifteen patients (53.4%) had normal chest X-ray findings, and seven patients (46.6%) had positive findings, with perihilar peribronchial thickening, poorly-defined nodular opacities, and pleural effusion in at least one patient. One patient (6.7%) had perihilar peribronchial thickening only, two patients (13.3%) had poorly-defined nodular opacities only, two patients (13.3%) had both perihilar peribronchial thickening and poorly-defined nodular opacities, and two patients (%13.3) had perihilar peribronchial thickening and poorly-defined nodular opacities with pleural effusion.

CT abnormalities were evaluated according to presence, type, distribution, and the extent of the disease, and additional CT findings were also recorded. Three of twelve patients (25%) had normal chest CT findings, and nine of twelve patients (75%) had positive findings, with ground-glass opacities (GGO), consolidation, pulmonary nodules surrounded by GGO, air bronchograms, with pleural and pericardial effusion findings observed in at least one patient. Of the nine patients with positive CT findings, seven (50%) had ground-glass opacities, seven (50%) had consolidation, six (41.6%) had both pulmonary nodules surrounded by GGO, and seven (41.6%) had air bronchograms. A crazy-paving pattern was identified in two patients (16.6%). Findings that were absent in all patients included bronchiectasis, cavitation, interseptal thickening, and fibrosis.

Table 1. Epidemiological and clinical characteristics of 15 patients with a confirmed Sars-CoV-2 infection.

	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**
Age (months)/Sex	42/M	122/F	168/M	122/F	75/M
Hematological baseline disease/ disease status	AML	Relapsed ALL	AML	Relapsed AML	ALL
Covid-19 symptoms/ Comorbidities	Dry cough, fever/ No	Asymptomatic (while performing pre-transplantation routine tests)/ No	Dry cough, fever/ No	Dry cough/ No	Dry cough, fever/ No
Site of patient care for Covid-19	Intensive care unit	home care	Covid-19 ward	Intensive care unit	home care
Evolution of signs and symptoms, complications	Fatigue, dyspnea, pneumonia	Stable clinical conditions	Stable clinical conditions	Stable clinical conditions, fatigue	Stable clinical conditions, fatigue
Covid-19 treatment	no respiratory support, hydroxychloroquine, Lopinavir/ritonavir, favipiravir	no respiratory support, hydroxychloroquine	no respiratory support, favipiravir	no respiratory support, hydroxychloroquine, Lopinavir/ritonavir, favipiravir	no respiratory support, hydroxychloroquine
First negative RT-PCR test, days from the diagnosis	35 days	8 days	14 days	46 days	14 days
Outcome	Resolved	Resolved	Resolved	Resolved	Resolved
	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Age (months)/Sex	118/M	216/M	210/F	46/F	200/M
Hematological baseline					

disease/ disease status	Relapsed ALL	ALL	CML	ALL (Relapsed disease)	AML
Covid-19 symptoms/ Comorbidities	Fever/ No	Dry cough, fever/ No	Fever/ No	Fever, cough/ No	Fever/ No
Site of patient care for Covid-19	Covid-19 ward	home care	home care	Intensive care unit	Covid-19 ward
Evolution of signs and symptoms, complications	Stable clinical conditions	Stable clinical conditions	Stable clinical conditions	Fever,cough, tachypnea, tachycardia, respiratory failure	Fatigue, dyspnea, pneumonia
Covid-19 treatment	Favipiravir	no respiratory support, hydroxichloroquine	no respiratory support hydroxichloroquine	Favipiravir, Methylprednisolone, Enoxaparin	Favipiravir, Methylpredniso lone
First negative RT-PCR test, days from the diagnosis	RT-PCR test is still positive	35 days	14 days	RT-PCR test has not become negative	21 days
Outcome	Resolved	Resolved	Resolved	Patient died	Resolved
	Patient 11	Patient 12	Patient 13	Patient 14	Patient 15
Age (months)/Sex	70/F	106/M	192/M	40/M	36/F
Hematological baseline disease/ disease status	ALL	Transplant patient (allogeneic HSCT Relapsed ALL)	Transplant patient (allogeneic HSCT, chronic granulomatous disease)	AML (posttransplant 640)	Relapsed ALL
Covid-19 symptoms/ Comorbidities	Fever/ No	Fever, cough/ GIS and cutaneous GVHD	Fever/ GIS GVHD	Asymptomatic/ No	Fever/ Cutaneous GVHD
Site of patient care for Covid-19	Covid-19 ward	Covid-19 ward, Intensive care unit	Covid-19 ward Intensive care unit	home care	Covid-19 ward
Evolution of signs and symptoms, complications	Fever,cough, tachypnea, tachycardia, respiratory failure	Fever,cough, tachypnea, tachycardia, respiratory failure	Fatigue, dyspnea, pneumonia	Stable clinical conditions	Fatigue, dyspnea, pneumonia
Covid-19 treatment	respiratory support, favipiravir	Favipiravir, Methylpredniso lone,enoxaparin	respiratory support, Favipiravir, Methylprednis olone,Enoxapa rin Convalescent plasma	no respiratory support, hydroxichloroqui ne	no respiratory support, hydroxichloroq uine
First negative RT-PCR test, days from the diagnosis	September 28, 2020 21 days	RT-PCR test has not become negative	No negative result	14 days	42 days
Outcome	Resolved	Died	Died	Resolved	Died

Table 2. Initial chest X-ray and CT examination findings of the patients.

Variable	
Chest X-ray finding	n (%)
Normal	9
Perihilar peribronchial thickening	1
Perihilar peribronchial thickening, poorly-defined nodular opacities, pleural effusion	3
Poorly-defined nodular opacities	2
Chest CT finding	n (%)
Bilateral involvement	4
Multilobar involvement	5
Localization Peripheral Central	 5 8
Opacities Ground-glass opacities (GGO) and consolidation Bronchiectasis Air bronchogram Pleural thickening	 6 0 6 5
Opacification distribution and pattern Rounded shape Linear opacities Crazy paving pattern Reverse halo sign Halo sign Peripheral distribution Cavitation	 2 0
Discrete pulmonary nodules	
Pleural effusion(s)	2
Lymphadenopathy	0
Pulmonary fibrosis	
Pneumothorax	0
Interseptal thickening	0
Normal	4

*M, male; F, female; ALL, acute lymphoblastic leukemia; AML, acute myeloblastic leukemia; sc, subcutaneous; GIS, Gastrointestinal system; GVHD, graft versus host disease; CML, chronic myeloid leukemia.

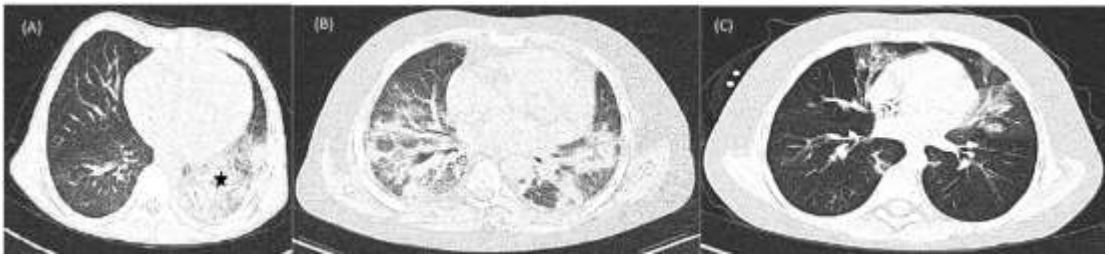

Figure 2. A) Patient no. 6, male (relapsed ALL). Chest CT showed diffuse areas of consolidation and ground-glass opacities in left lung and a "white lung" appearance of the left lung. B) Patient no. 3, male (allogeneic HSCT, chronic granulomatous disease). Chest CT showed scattered opacities and mild perihilar bronchial enlargements in both lungs with near-total ground-glass appearance. C) Patient no. 12, male (allogeneic HSCT Relapsed ALL). Chest CT showed scattered ground-glass opacities in the inferior lobe of the right lung, located subpleural or extended from subpleural lesions.

Among twelve patients evaluated with chest CT scans, three patients (25%) had findings with only peripheral lung distribution, three patients (25%) had findings with only central lung distribution, and three patients (25%) had findings with both peripheral and central lung distributions.

Multilobar involvement was identified in six patients (50%).Among nine patients (75%) with positive chest CT findings, four had unilateral disease (one had left lung involvement only, and three had right lung involvement only), and five patients had bilateral disease. Two patients (16.6%) had pleural effusion, and five patients (41.6%) had pericardial effusion. Findings that were absent in all patients included lymphadenopathy, pleural thickening, and pneumothorax.

Blood test results were available for all patients. Lymphocyte values were below normal (<1500/μL) in six patients. These patients also had neutropenia (<1500/μL). Eight patients (53.3%) had an elevated CRP (>0.79 mg/dl).

On average, eight days (min. 0, max. 24 days) before COVID-19 diagnosis, 11 patients received chemotherapy. Two patients (numbers 6 and 10) had recently undergone an HSCT. Nine patients had been treated with active chemotherapeutics, one with cyclosporin A, one with tacrolimus and ruxolitinib, one with sirolimus and methylprednisolone, and one with ruxolitinib alone. The majority of patients (n=6) did not need hospitalization for COVID-19 treatment, but three of the patients were treated in the ICU and four patients were monitored at home. Three patients treated in the COVID-19 ward required mechanical ventilation and were transferred to the ICU due to a deterioration in their clinical condition and later succumbed to the disease. Antiviral treatment was applied according to the pediatric COVID-19 guidelines from the Ministry of Health, which is constantly updated at regular intervals. While hydroxychloroquine was preferred as monotherapy in the initial period of the pandemic, lopinavir/ritonavir and favipiravir were also recommended for second and third-line treatment later on. All patients with pneumonia (as well as febrile neutropenia) (n=8) received broad-spectrum antibiotics. Seven patients received hydroxychloroquine, one received favipiravir, four received favipiravir + methylprednisolone, two received hydroxychloroquine + lopinavir/ritonavir + favipiravir, and one received hydroxychloroquine + lopinavir/ritonavir + favipiravir + enoxaparin. In addition, broad-spectrum antibiotics were administered to patients with bacterial superinfection. In addition, the treatment was modified following identification of positive effects due to anticoagulant therapy and corticosteroids on the prognosis in patients who needed advanced respiratory support.

The average time to a negative RT-PCR test result for COVID-19 was 19 days. Four patients died while still positive. The patients' chemotherapy was delayed in all 15 patients. One ALL and one AML patient (patient numbers 1 and 11, respectively), whose treatment was delayed due to COVID-19 infection, developed relapsed/refractory disease.

Three of the patients (20%) were followed up in the ICU, six patients (40%) in the isolated COVID ward, and six patients (40%) were monitored at home under isolation. Two of the patients were monitored in a COVID ward (patients 6 and 12) but were transferred to intensive care due to a deterioration of their clinical condition and a need for mechanical ventilation.

All patients, except those who died, are still being monitored in relation to primary hematological diseases and are in remission for COVID-19.

DISCUSSION

In this study, we aimed to evaluate the clinical and radiological characteristics and the treatment approach of COVID-19 infection in pediatric hemato-oncological and transplant patients who received active chemotherapy or immunosuppressive treatment. Studies examining the same issue in pediatric hematological patients have been reported recently[16,17]. However, it has been difficult to treat hemato-oncological diseases during the COVID-19 pandemic. Each center has developed its own approach to follow-up treatment in this short period for a limited number of patients, given that COVID-19 is a newly defined disease and there is no consensus on the approach to follow in pediatric hemato-oncological patients infected with Sars-CoV-2.

Although a positive RT-PCR for Sars-CoV-2 nucleic material in a patient's respiratory or blood sample is necessary, some confirmed cases may yield negative results.

It is known that lung imaging is required in patients with COVID-19 infection. However, it is a fact that

typical lung CT findings are detected less frequently in pediatric patients[18]. In addition, abnormal chest CT images do not always indicate COVID-19 pneumonia, as children with hemato-oncological malignancies receive chemotherapy and often have pneumonia due to immunosuppression[19]. In our study, the findings on chest CT in children were mainly milder than in adults. Unilateral or bilateral subpleural ground-glass opacities, consolidations, and air bronchograms were the most typical appearances. Chest CT findings were also serious, as immunosuppression was more severe in patients receiving active intensive chemotherapy, especially in patients who had undergone HSCT (Table 2, Figure 2). A limited number of studies have been published that evaluated the clinical status and CT images in COVID-19 infected pediatric cancer patients[20]. Chest CT imaging of 11 of the patients (84.6%) with positive COVID-19 RT-PCR test results was suggestive for COVID-19 pneumonia. There was only one patient who had a negative RT-PCR test and was diagnosed on the basis of clinical findings and lungs showing signs typical of COVID-19. COVID-19-related chest CT changes may occur before the onset of clinical symptoms[1], or chest CT abnormalities may occur in patients who test negative via RT-PCR for COVID-19[21,22]. Considering that thoracic direct radiography findings of neutropenic patients may be subtle or normal, we believe that thorax CT imaging should be performed in every patient with a suspected or confirmed positive RT-PCR test result in this patient group.

A small infection rate (0.1%) can be seen in our study due to the total percentage of confirmed cases of COVID-19. However higher rates were reported in pediatric patients previously[23]. This low rate can be explained by the increase in the number of tests carried out, especially in recent months. Each patient was tested as part of screening even if he or she was hospitalized in our clinic with different indications. In addition, the fact that we maintained a very low suspicion threshold may be one of the reasons for this situation.

While infectious cases in children are often asymptomatic or resolve following mild to moderate symptoms, it was observed in our study that the clinical course was more severe and more likely to result in death in patients who were immunosuppressed as a result of chemotherapy. The most significant difference in patients who do not have an underlying immunosuppressive condition is the duration of RT-PCR test positivity in patients receiving chemotherapy. While this period was 46 days for patient number 4 (relapsed AML), who was given active chemotherapy treatment, and 35 days for patient number 1 (AML), patient number 6, who had undergone a transplant and received sirolimus plus methylprednisolone in a course of immunosuppressive treatment, was found to be continuously positive until their death. Similarly, the RT-PCR test remained positive for 22 days for patient number 12, who received immunosuppressive therapy with tacrolimus and Jakafi for chronic GIS and cutaneous GVHD; the patient later died. Patient number 14's (relapsed ALL) RT-PCR test also remained positive, and the patient died on day 26. The observation that patients suffered more severe COVID-19 infection in the study conducted by Andre et al. with 33 pediatric hematology-oncology patients also supports our findings[24], since five (15%) of the 15 patients included in this study had to be admitted to an ICU, and one patient died as a result of COVID-19 complications. Again, in a study conducted in adult COVID-19 patients diagnosed with cancer, the results showed that, in line with the results of previous studies, mortality in infected cancer patients was significantly increased compared to Sars-CoV-2-infected patients without comorbidities[25]. Recent studies in adults have also shown higher mortality rates among cancer patients with serious Sars-CoV-2 infection[26]. The clinical and radiological characteristics of immunocompromised children with COVID-19 infection appear to be similar to those of adult patients[27]. A few studies also exist which claim otherwise: Rojas et al. conducted a study on 15 children with malignancy and found that COVID-19 infection was milder and the prognosis was better compared to adult patients[28].

Among patients that required admission to an ICU and later died from COVID-19, one was a 14-year-old boy undergoing immunosuppressive therapy for cutaneous GVHD following HSCT for immune deficiency. His respiratory state deteriorated and he was transferred to the ICU, where he developed various problems, including respiratory failure, which contributed to his death. The second was a four-year-old girl undergoing chemotherapy for relapsed ALL. The patient presented at our clinic with neutropenic fever and subsequently tested positive for SARS-CoV-2; the patient developed respiratory failure due to pneumonia and died. The last patient was a 9-year-old boy who was receiving tacrolimus and Jakafi for

GVHD after HSCT for relapsed ALL. However, in studies conducted by Gampel et al. (with 19 COVID-19-positive pediatric hemato-oncological patients), and by Faura et al. with 47 such patients, only three (one patient diagnosed with sickle cell disease and two that had received an allo-SCT and had graft-versus-host disease) were observed[23,27]. The only patient diagnosed with sickle cell disease in our study was a 16-year-old boy who developed respiratory failure associated with COVID-19 but recovered within ten days. There is no distinct reason for these differences (treatment modality, hospital conditions, medications) between our report and these studies. The fact that the studies were carried out in different periods, the change of treatment approaches over time, the different COVID-19 management model among health centers, the difference in ICU conditions between health centers and patient-specific situations can be seen as causative factors. Male patients in our sample were more likely to suffer from serious illnesses. There are other studies with results that are consistent with our findings[23-28], as well as publications with contradictory results[3]. However, there are still unexplained mechanisms behind the observed differences between male and female patients. The protective effect of estrogen receptors against Sars-CoV infection in females is thought to be the cause of this result[29], but there are still unexplained mechanisms behind the identified difference between the sexes.

It is not clear if patients' outcomes were affected by these therapies. Patients that were admitted to the ICU received methylprednisolone and anticoagulant (enoxaparin) therapy, as well as antiviral (favipiravir) therapy. Only oral antiviral therapy was initiated in patients diagnosed with ALL who received maintenance treatment and were monitored at home. Owing to this limited number of patients, it is hard to evaluate the findings; however, no complications related to COVID-19 were observed in any of the patients monitored at home. Antiviral treatment selection was performed according to the COVID-19 treatment guide, which is constantly updated according to current guidelines.

10 of the 15 fifteen patients had their primary disease-directed treatments delayed due to the COVID-19 pandemic. Most of the chemotherapy delays were due to planned treatment delays, not COVID-19 complications. Even if the symptoms of the patients were mild, all chemotherapy and immunosuppressive treatments were stopped or delayed. However, there are also health centers that continue to administer chemotherapy for some patients without any complications[17]. As a general rule, timely administration of cancer chemotherapy is essential, and this research may not provide any clear advice for oncological treatment. However, it may be a good idea to choose the low/medium risk group, or the group that is not subject to an intensive chemotherapy/immunosuppressive regimen, in patients infected with Sars-CoV-2 with cancer who will be given chemotherapy (this author's opinion). Alternatively, another approach may be to postpone non-urgent hemato-oncological treatments until patients test negative for Sars-CoV-2, which seems to be the consensus among most healthcare professionals[17]. Some authors advocate for the idea that cancer treatment can be given in hemato-oncological patients who have no underlying diseases beyond their primary disease[23]. In our study, patient number 1, diagnosed with AML, contracted COVID-19 while in remission after the second course of induction chemotherapy. Therefore, the continuation of the patient's treatment was delayed for 35 days. In the bone marrow evaluation performed after the infection, it was observed that he was not in remission. A salvage chemotherapy regimen was administered, but the patient died of sepsis. As such, a delay in the treatment of the primary disease in hemato-oncological patients with COVID-19 can also be counted among the complications of COVID-19.

Hospitalized COVID-19 patients may have lymphopenia, coagulation disorders, high levels of D-dimer, and troponin. No specific changes in laboratory parameters were recorded in our 15 patients with COVID-19 during the viral infection. It should be noted that it is not easy to evaluate laboratory data in hemato-oncological patients undergoing active chemotherapy and/or immunosuppressive therapy due to myelosuppression, non-COVID-19 infections, steroid effects, adverse effects of drugs, or cancer coagulopathy.

One of the most striking points in our study is the prolongation of Sars-CoV-2 RT-PCR positivity in patients with chemotherapy-induced myelosuppression or who are receiving immunosuppressive therapy. In the study conducted by Cento et al. involving 7,608 adult patients with COVID-19 infection, it was observed that RT-PCR

positivity was prolonged to between 41 to 60 days in 14.7% of patients after hospital discharge[30].

In studies related to laboratory parameters of COVID-19 patients, it is frequently observed that low total leukocytes, lymphocytes, and eosinophil values were detected[31]. However, similar laboratory findings were not encountered except in our patients who received active chemotherapy. Since COVID-19 infection was complicated with neutropenic fever in patients receiving chemotherapy, it was not possible to associate low complete blood count values with COVID-19 infection.

Although some of our patients had positive chest X-ray findings, these results were given secondary priority as compared to chest CT (especially in neutropenic patients) because their radiological patterns were nonspecific and had no diagnostic value as reported in the literature[32].

The limitation of our study is that the number of patients included in the study is low due to the small number of pediatric COVID-19 cases in hemato-oncological clinics. The lack of statistical power analysis for the sample size can be considered as another limitation of our study.

In conclusion, to develop precise guidelines for prophylaxis and treatment of Sars-CoV-2 infection and disease in hematological patients, there is still a lack of evidence. There is currently no guideline or clear data available for prophylaxis and treatment of Sars-CoV-2 infection in hematological patients. The fact that an effective vaccine has just been found and the duration of the pandemic cannot be predicted, drawing attention to take an additional measure, especially in patients with COVID-19 infection with additional diseases such as malignancy.

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