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LETTER TO THE EDITOR

Initial report on Spanish pediatric oncologic, hematologic, and post stem cell transplantation patients during SARS-CoV-2 pandemic

To the Editor:

In December 2019, the SARS-CoV-2 outbreak started in China and rapidly progressed into a pandemic.[1] Spain was one of the first countries in Europe reporting increasing numbers of both confirmed cases and deaths. As of April 24, 2020, 202 990 cases had tested positive and 22 524 deaths were reported due to COVID-19. The clinical presentation of COVID-19 may range from asymptomatic cases to severe forms.[2] In contrast, pediatric patients rarely develop critical illness.[3,4] In Spain, cases under the age of 19 represented only 0.9%. Furthermore, only 2.8% of these cases required pediatric intensive care unit (PICU) admission with a mortality rate of 0.3%.[5] Children diagnosed with cancer under immunosuppression have a higher risk for opportunistic infections. To this date, reports describing the clinical and epidemiological characteristics of this collective with COVID-19 are scarce. A survey in Europe of SARS-CoV-2 infections in pediatric patients with anticancer treatment identified only nine patients with mild infections.[6] A reasonable fear exists that SARS-CoV-2, like other coronaviruses,[7] could cause more severe infections in immunocompromised children, as has been observed in adults with cancer.[8,9]

We surveyed all Spanish institutions treating pediatric cases (1 month-18 years of age), with solid and hematologic malignancies, nonmalignant hematologic conditions receiving immunosuppressive treatment or bone marrow failure syndrome and after allogeneic-stem cell transplantation (allo-SCT), or CAR T-cell therapy who were diagnosed with COVID-19 from January 31 to April 24, 2020. Information was received from 41 hospitals (representing 97.6% of pediatric cancer patients in Spain).[10] All data related to RT-PCR confirmed SARS-CoV-2 infection of 47 cases are summarized in Table 1. We observed a male predominance (72.3%), with the majority of cases having leukemia or lymphoma (51.5%). Six patients with severe nononcologic hematologic conditions under immunosuppressive therapy were included. Three patients had received CAR T-cell therapy as salvage regimen for relapsed B-ALL. The majority of patients were asymptomatic (25.5%) or had only mild symptoms (51.1%). Radiologic abnormalities were observed in 32.4% of the patients. Thirty-two patients required hospitalization (76.6%). However, 12 of them were already admitted when COVID-19 diagnosis was made. Severe illness was identified in 11 patients. Four of them (all males) evolved to critical illness with progressive respiratory failure requiring admission to the PICU (8.5% of all patients). Two of them died of COVID-19-related complications. Both cases had received an allo-SCT and had graft-versus-host disease (GVHD). One of them had also received CAR T-cell therapy. Regarding abnormal laboratory findings, critically ill patients presented in a higher frequency with severe lymphopenia (medians: 85/mm^3 vs 1000/mm^3, $P = .0034$) and higher ferritin levels at diagnosis (medians: 6667 ng/mL vs 1037 ng/mL, $P = .027$). The maximum ferritin level was also significantly superior in patients admitted to the PICU (medians: 23 077 ng/mL vs 1508 ng/mL, $P < .001$). Asymptomatic/mild cases (44.6%) did not receive any therapy. Twenty-three patients received hydroxychloroquine (nine combined with azithromycin), followed by antivirals (19.1%) and corticosteroids (6.4%). Six patients received monoclonal antibodies against IL1/IL6. Anticancer therapy was interrupted in 57.9% of the cases. Prophylactic anticoagulation was administered to five patients (10.6%), with no thromboembolic events diagnosed.

Respiratory viral infections in immunosuppressed patients usually present a more severe clinical evolution and higher mortality rate,[11] including HCoV cases.[12] In our country, 1300 children and adolescents are diagnosed with cancer every year.[10] Including only cancer diagnosis, we observed a COVID-19 infection rate of approximately 2.5% among this patient population. Most of the reported patients (68%) were from the states of Madrid and Catalonia, the two most affected areas in Spain.[13] Fifteen of the patients included in the present study were previously reported recently by de Rojas et al.[14] Initial experiences from Italy (Lombardy),[15] China (Wuhan),[16,17] and Europe suggest a low number and severity of COVID-19 cases in this patient population,[6] contrary to France, where a higher incidence of critical patients was observed.[18] Although in our case series, majority of patients were asymptomatic (25%) or had a mild course (51.1%), the percentage of critical patients (23.4%) was higher in comparison to the Chinese cohort (3-10.6%).[3] Moreover, the PICU admission rate was 8.5% in our study, higher to that observed in the general pediatric population.[19] Of note, all four critical patients were either receiving intensive chemotherapy or severely immunosuppressed post allo-SCT. Noteworthy, low total lymphocyte counts and high ferritin levels at onset of symptoms were observed in cases admitted to the PICU. One of the deaths in the post allo-SCT subgroup was probably related to an uncontrolled systemic inflammatory response that closely resembled a macrophage activation syndrome, as has been described.[20] In our cohort, no diagnosis of Kawasaki-like disease was identified as described elsewhere.[21]

TABLE 1 Demographic data, underlying diagnosis, clinical features, therapy received, and outcome of 47 patients with SARS-CoV-2 confirmed infection

Characteristics		N
Age		47
Mean (standard deviation)	*8.2 (4.7)*	
1 year or less	6 (13%)	
2-5 years	9 (19%)	
6-10 years	15 (32%)	
11-14 years	13 (28%)	
15-18 years	4 (8%)	
Sex		47
Male	34 (72%)	
Female	13 (28%)	
Type		47
Nonmalignant hemopathy[a]	6 (13%)	
Solid tumor	14 (30%)	
Leukemia/lymphoma non-HSCT	19 (40%)	
Post-HSCT	8 (17%)	
Phase		41
First line	33 (80%)	
Relapse	8 (20%)	
Severity of illness		47
Asymptomatic	12 (26%)	
Mild	24 (51%)	
Serious	7 (15%)	
Critical	4 (8%)	
Radiological image performed		47
Yes	37 (79%)	
No	10 (21%)	
When performed:		37
Normal	25 (68%)	
Unilateral pneumonia	6 (16%)	
Bilateral pneumonia	6 (16%)	
Need for hospitalization		47
Hospital care	32 (77%)	
Critical care (ICU)	4 (8%)	
Respiratory support		
Conventional oxygen therapy		47
Yes	8 (17%)	
No	39 (83%)	
High-flow/noninvasive ventilation		47
Yes	3 (6%)	
No	44 (10%)	
Mechanical ventilation		47
Yes	2 (4%)	
No	45 (96%)	
Treatment		
Hydroxychloroquine		47
Yes	23 (49%)	
No	24 (51%)	
Antiviral		47
Yes	9 (19%)	
No	38 (81%)	
Monoclonal antibody		47
Yes	6 (13%)	
No	41 (87%)	
Interruption of baseline treatment:		46
Yes	22 (48%)	
No	24 (52%)	
Clinical evolution		47
Alive and resolved	31 (66%)	
Alive, with active infection	15 (32%)	
Exitus	1 (2%)	

[a]Autoimmune hemolytic anemia (one patient), sickle cell disease (one patient), bone marrow failure (2 patients), primary immune thrombocytopenia (one patient), hemophagocytic lymphohistiocytosis (one patient).

Regarding therapy, hydroxychloroquine and antivirals were used mainly in early stages.[22] In those with a more aggressive disease and/or hyperinflammation component, immunomodulatory treatments were administered.[23] Specific treatment recommendations should be available soon with ongoing basic and clinical trials progress.[24] According to our data, most patients will have a good outcome. However, patients receiving intensive chemotherapy, severely immunosuppressed, or GVHD may be at a higher risk of morbidity and even mortality. During this pandemic, concern exists whether children with cancer may present late for diagnosis or not receive appropriate oncological treatment.[25,26] In our cohort, half of the patients interrupted their anticancer treatment due to the infection. Recent guidelines published[27] for children with cancer recommend that the standards of care should not be compromised during the pandemic. We recommend individualized multidisciplinary discussions whenever a COVID-19 case is identified for deciding on interrupting or delaying anticancer therapy.

Limitations of this report include the small sample size retrospective data collection. However, since most of Spanish PHO units took part in this initiative, we believe our report represents an accurate infection prevalence among this population at a national level. This is one of the largest series of COVID-19 in pediatric cases with solid and hematological malignancies, benign hematologic conditions, and post allo-SCT, observing that most patients present a favorable clinical evolution. However, severe forms of infection can be seen in highly immunosuppressed patients, in those with chronic comorbidities such as GVHD, or patients receiving CAR T-cell therapy.

AUTHOR CONTRIBUTIONS

This is a collaborative SEHOP initiative. Anna Faura, José Luis Dapena, Susana Rives, and Andrés Morales La Madrid were involved in designing the study. All authors were involved with patient accrual and data collection. Sara Perez-Jaume was the statistician of the study. Anna Faura, José Luis Dapena, Sara Perez-Jaume, Susana Rives, and Andrés Morales La Madrid were involved with data interpretation. All authors contributed to the manuscript editing and approved the final manuscript. Andrés Morales La Madrid and José Luis Dapena contributed equally to this work.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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