Journal of Clinical Immunology (2021) 41:1523–1526
https://doi.org/10.1007/s10875-021-01094-4

LETTER TO EDITOR

Containment of Local COVID-19 Outbreak Among Hematopoietic Stem Cell Transplant Recipients and Healthcare Workers in a Pediatric Stem Cell Unit

Monia Ouederni[1,2] · Samia Rekaya[1,2] · Oussema Bouabdallah[1,2] · Ilhem Ben Fradj[1,2] · Ridha Kouki[1] · Yosr Chebbi[2,3] · Sahar Ben Ammar[1] · Takwa Lamouchi[1] · Asma Lachiheb[1] · Nessrine Zekri[1] · Siwar Laajili[1] · Ikram Zaiter[1] · Agnes Hamzaoui[2,4] · Mohamed Bejaoui[1,2] · Fethi Mellouli[1,2] · Wafa Achour[2,3] · Monia Ben Khaled[1,2]

Received: 16 February 2021 / Accepted: 3 July 2021 / Published online: 15 July 2021

Background

The pandemic coronavirus SARS-CoV-2 poses unprecedented stress on the hematopoietic cell transplantation (HSCT) centers. Immunological recovery after HSCT is habitually required for infection control [1]. However, the natural history of the SARS-CoV-2 in pediatric patients receiving HSCT is largely unknown. Furthermore, the transplantation units are facing many other challenges related to HSCT planning and the risk of SARS-CoV-2 spread among healthcare personnel. A traceable outbreak of SARS-CoV-2 among healthcare workers at an adult HSCT unit was recently reported affecting five nurses [2]. Few separated case reports of SARS-COV2 were published in children receiving HSCT [3, 4]. We report on an outbreak of COVID-19 among healthcare workers and patients at a pediatric HSCT unit, measurements taken for its containment, and the outcome of pediatric HSCT recipients diagnosed with SARS-CoV-2 infection. This is, to our knowledge, the first report of the SARS-CoV-2 outbreak in a pediatric HSCT unit.

✉ Monia Ouederni
ouederni.moni@gmail.com

1 Department of Pediatrics: Immuno-Hematology and Stem Cell Transplantation, Bone Marrow Transplant Center, Tunis, Tunisia

2 Faculty of Medicine, University of Tunis El Manar, Tunis, Tunisia

3 Laboratory of Microbiology, Bone Marrow Transplant Center, Tunis, Tunisia

4 Department of Pneumology, Abdurrahman Memi Hospital, Tunis, Tunisia

Methods

The pediatric HSCT unit being reported on has 16 single bedrooms. Five rooms, equipped with a high efficiency particulate air (HEPA) filter positive pressure lock system, are reserved for HSCT recipients. Eleven beds, placed in single-patient rooms with ambient air, are used for pre-transplant management of children with primary immunodeficiencies, hematological disorders, and post-transplant management of late HSCT complications.

Specific procedures of the unit impose protective isolation of patients with the wearing of surgical masks and overshoes before entering the inpatient room and the wearing of gloves before any direct patient contact. Visits are forbidden in the HEPA filter rooms, and patients are not allowed to leave their rooms. These procedures have been strengthened during the SARS-CoV-2 pandemic, as have been addressed by the recent EBMT recommendations [5] including training of staff on proper procedures. Accompanying mother should wear surgical mask and gown in the patient room, in addition to gloves before any direct patient contact.

After the detection of the first case of SARS-CoV-2 in the unit on September 4, 2020, all healthcare workers, patients, and their accompanying persons were screened for SARS-CoV-2 via a real-time polymerase chain reaction (RT-PCR) from nasopharyngeal swabs regardless of whether upper respiratory symptoms are present. This was justified by the high immunocompromised nature of hospitalized patients.

Results

Among healthcare workers, 15 out of 53 tested positive for SARS-CoV-2 according to RT-PCR (three physicians, four training students, four nurses, and four cleaning workers).

Two out of 16 accompanying mothers also tested positive for SARS-CoV-2. SARS-CoV-2 infection was diagnosed in five patients, confirmed by positive RT-PCR in four patients and by Chest CT scan in one patient.

Infection occurred after HSCT in three of the five SARS-CoV-2 positive patients. Characteristics of transplanted patients are summarized in Table 1. The first case was a 7-year-old boy who underwent HSCT for severe acquired bone marrow failure. He had a partially controlled invasive blastomycosis. On day 60 post-HSCT he exhibited fever, diarrhea, cough, dyspnea, and hypoxia. SARS-CoV-2 was detected in his mother having minor flu-like symptoms. Repeated SARS-CoV-2 RT-PCR of the patient was negative. The chest CT scan showed new images consistent with COVID-19–associated pneumonia. Other respiratory viral pathogens were negative by multiplex PCR. He had normal neutrophils level and profound lymphopenia. Azithromycin and nasal oxygen were prescribed. All signs disappeared 5 days later. CT scan showed no new images with regression of pulmonary ground-glass opacities 14 days later. The second case of SARS-CoV-2 was detected in a 6-year-old girl 7 days after HSCT for severe congenital neutropenia. She received haploidentical T-replete HSCT with post-transplant cyclophosphamide. Neutrophils and lymphocytes were absent. She exhibited abdominal pain with diarrhea without fever nor respiratory signs. She received oral azithromycin. The patient was kept in her single room in the HSCT unit. Two RT-PCR tests came back negative 7 days, and 10 days later, her mother had a negative RT-PCR. The third case was a 16-year-old boy who underwent HSCT from MSD for Shwachman-Diamond syndrome with myelodysplasia. He had chronic pulmonary GVHD. Nine months after HSCT, positive RT-PCR was detected due to the positivity of a close contact relative. He exhibited headaches and a dry cough, but he had no exacerbation of the other baseline respiratory signs. Chest CT showed no new images. He was treated as an outpatient with azithromycin and home monitoring of SpO2, while no hospitalization was required.

Infection occurred before HSCT in the other two patients. The fourth case was an 18-month-old patient having juvenile myelomonocytic leukemia. He had neither respiratory nor digestive signs. Chemotherapy was delayed, and he was discharged. His RT-PCR came back negative 14 days later. The fifth case was a 5-year-old girl having inherited myelodysplasia and monosomy 7 due to SAMD 9 mutation. She was admitted for haploidentical HSCT. SARS-CoV-2 was detected by RT-PCR, and she had a transient mild fever and cough. Her chest CT scan was normal. The HSCT was delayed and 14 days later her RT-PCR was negative.

All the other patients had negative RT-PCR. SARS-CoV-2 was detected in an asymptomatic mother whose 13 months old, breastfed son had an aplasia after chemotherapy for acute lymphoblastic leukemia. He was asymptomatic and his RT-PCR was still negative during controls. Positive mothers were discharged. All positive healthcare workers stopped working. The negative healthcare persons continued to work with strict hygiene measures, dedicated persons for positive patients using individual protective equipment and grouping of care. Inpatients were tested for SARS-CoV-2 as soon as any symptoms indicative of COVID-19 developed. All new patients and accompanying mothers were tested for SARS-CoV-2 before admission. HSCT was delayed 2 weeks and restarted after decontamination of spaces. Outpatient visits were substituted with telemedicine when feasible. By December 5, 2020, all tests remained negative, and no new case of COVID-19 was detected among hospitalized patients.

Discussion

In this report of SARS-CoV-2 screening in a pediatric HSCT unit, few patients were positive, despite that several healthcare workers were infected. Few separated cases of pediatric HSCT recipients have been reported so far during the pandemic [3, 4]. Among 92 COVID-19 infected PID patients, three pediatric cases were HSCT recipients [6]. A report from the French pediatric oncology centers has identified two HSCT recipients among 33 COVID-19 infected patients [7]. It has been hypothesized that different surveillance strategies could explain the low rate of infection in pediatric HSCT recipients. However, in our center, all patients were screened regardless of the presence of signs. It could also reflect more restrictive isolation approaches in HSCT units. Urgent measures taken permitted the containment of COVID-19 spread and probably reduce the viral load [5]. In addition, the sensitivity of RT-PCR in allografted, immune-deficient, and aplastic patients is controversial. A negative PCR does not rule out the possibility of infection. The diagnosis was made on CT signs in one patient, whose mother had positive RT-PCR. CT scan results have been described to have a high sensitivity [8]. However, after HSCT, clinical and radiological manifestations are not specific to COVID-19, and common differentials like fungal and other viral infections should be considered. Assigning the responsibility of respiratory signs to COVID can also be difficult to hold in the presence of underlying lung disease such as GVHD in one patient. Comparison to baseline signs is crucial in these patients. Diarrhea observed could be due to COVID. However, gastrointestinal symptomatology can easily be confused with other differentials like acute gut GVHD, CMV colitis, and mucositis [6].

Furthermore, there was no severe form of COVID 19 infection among the pediatric HSCT recipients despite immunocompromised status. Severe forms were reported in adult HSCT recipients with a high mortality rate

Table 1 Characteristics of pediatric HSCT recipients diagnosed with SARS COV2 infection

	Age	Sex	Dg	Type	Condit	Time	Symptom/source of infection	Disease status at COVID	Comorbidities GvHD	Immunosuppression	Other Concomitant medication	Outcome
P1	7 years	M	SAA	MSD	ATG, Flu, Cy	60 days	Fever, cough, hypoxia, dyspnea/inpatient, mother COVID positive	Engraftment, PNN3400/mm3, Lymphopenia CD19 + 0, CD3 + 188, CD4 + 21, CD8 + 146, NK cells 211/mm3	Cutaneous GvHD Chronic pulmonary blastomycosis	CSA, CS	Immunoglobulins, Voriconazole, acyclovir, heparin, levofloxacin	Alive
P2	6 years	F	SCN	Haplo-SCT	ATG, Bu, Flu, PT-Cy	7 days	Diarrhea, abdominal pain/inpatient	Profound aplasia, PNN 0/ lym 0/ mm3	-	CSA, CS MMF,	Heparin, fungizone, acyclovir	Alive
P3	16 years	M	SDBS, MDS	MSD	ATG, Bu, Flu	9 months	Headache, Cough No new signs/outpatient, mother COVID positive	Engraftment, cured MDS, PNN 2600/mm3, Lymphopenia CD19 + 70; CD3 + 480; CD4 + 195, CD8 + 280; NK cells 85/mm3	Chronic pulmonary GVHD	MMF, CS	Voriconazole, acyclovir, amoxicillin	Alive

Dg diagnosis, *SCN* severe congenital neutropenia, *SAA* severe aplastic anemia, *SDBS* Shwachman-Diamond syndrome, *HSCT* hematopoietic stem cell transplantation, *type* type of BMT, *Condit* conditioning regimen, *time* time from HSCT to COVID-19 diagnosis, *haplo-SCT* haploidentical stem cell transplantation, *MSD* matched sibling donor, *MDS* myelodysplasia, *Flu* fludarabine, *Cy* cyclophosphamide, *PTCy* post-transplant cyclophosphamide, *Bu* busulfan, *ATG* antithymocyte globulins, *PNN* neutophiles, *GvHD* graft versus host disease, *MMF* mycophenolate mofetil, *CSA* ciclosporin A, *CS* corticosteroids

nearing 28% that can be directly attributed to COVID-19 [9]. Mild forms in pediatric HSCT recipients might reflect what is observed in the general population. However, the occurrence of a multisystemic hyperinflammatory syndrome in children has challenged this perception [10]. The few publications so far showed a very low incidence of complications in transplanted patients infected by SARS-Cov-2 that could be a result of an immune system not capable of triggering a major inflammatory response [3, 4, 6, 7]. In the ESID report, one child died. He had severe gut GVHD. Thus, it was unclear how much SARS-CoV2 contributed to the death [6]. It is also important to mention that all our patients had lymphopenia. Thus, a certain component of adaptive immunity does not appear to be essential for controlling SARS-CoV2 infection. Rather, adaptive immune deficiencies may even contribute to a milder course by reducing the cytokine release syndrome (CRS) and the excessive tissue damage [11]. Neutrophils do not also appear to be essential for controlling SARS-CoV2 infection in these patients. Our patient is one of the rare reported pediatric cases of SARS-CoV-2 infection successfully recovered during the early period of profound bone marrow aplasia [3, 4]. Moreover, PTCy received by this patient could contribute to milder form as previously reported in four adults. The PTCy mediates alloreactive T cell elimination, induces T-regulatory cell expansion, and abrogates CRS in haploidentical HSCT that looks like the severe COVID-19-associated CRS [9]. Two of our patients were receiving corticoids; this might have had beneficial effects on inflammation too [10]. Given that all cases were mild, no specific drugs were used, and patients were kept in the unit. The transfer of patients during the peri-transplant phase is not recommended unless not otherwise manageable life-threatening conditions occur [5]. Thus, all the efforts were made to keep the HSCT unit, free from circulating SARS-CoV-2.

In this experience of the SARS-CoV-2 outbreak in a pediatric HSCT unit, the application of the COVID-19 risk management strategy according to the EBMT recommendations permitted to stop local epidemic among patients despite the fact that many healthcare workers were affected. Furthermore, all allograft pediatric recipients have exhibited mild COVID-19 despite immunocompromised status, underlying lung disease, and profound aplasia. Thus, a certain component of adaptive and innate immunity does not appear to be essential for controlling SARS-CoV2 infection in these patients. Rather, post-transplant induced immune deficiency and even more PTCy may even contribute to a milder form by reducing the CRS. The long-term consequences of COVID-19 in children receiving HSCT remain unclear. Further studies are needed to advance the knowledge of the scientific community, especially HSCT practitioners, of this new disease.

Acknowledgements We acknowledge all healthcare workers in the pediatric HSCT unit, the patients, and their families.

Declarations

Informed Consent Consentement was obtained from all participants.

Conflict of Interest The authors declare no competing interests.

References

1. Broxmeyer HE, Parker GC. Impact of COVID-19 and future emerging viruses on hematopoietic cell transplantation and other cellular therapies. Stem Cells Dev. 2020;29(10):625–6. https://doi.org/10.1089/scd.2020.0064.
2. Buchtele N, Rabitsch W, Knaus HA, Wohlfarth P. Containment of a traceable COVID-19 outbreak among healthcare workers at a hematopoietic stem cell transplantation unit. Bone Marrow Transplant. 2020;55(7):1491–2. https://doi.org/10.1038/s41409-020-0958-6.
3. Zamperlini-Netto G, Fernandes JF, Garcia JL, Feitoza Ribeiro AA, Aranha Camargo LF, Terra CM, et al. COVID-19 after hematopoietic stem cell transplantation: report of two children. Bone Marrow Transplant. 2020. https://doi.org/10.1038/s41409-020-01041-8.
4. Jarmoliński T, Matkowska-Kocjan A, Rosa M, Olejnik I, Gorczyńska E, Kałwak K, et al. SARS-CoV-2 viral clearance during bone marrow aplasia after allogeneic hematopoietic stem cell transplantation, a case report. Pediatr Transplant. 2020;18:e13875. https://doi.org/10.1111/petr.13875.
5. Ljungman P, Mikulska M, de la Camara R, Basak GW, Chabannon C, Corbacioglu S, et al. The challenge of COVID-19 and hematopoietic cell transplantation; EBMT recommendations for the management of hematopoietic cell transplant recipients, their donors, and patients undergoing CAR T-cell therapy. Bone Marrow Transplant. 2020;55(11):2071–6. https://doi.org/10.1038/s41409-020-0919-0.
6. Meyts I, Bucciol G, Quinti I, Neven B, Fischer A, Seoane E, et al. Coronavirus disease 2019 in patients with inborn errors of immunity: an international study. J Allergy Clin Immunol. 2021;147(2):520–31. https://doi.org/10.1016/j.jaci.2020.09.010.
7. André N, Rouger-Gaudichon J, Brethon B, Phulpin A, Thébault E, Pertuisel S, et al. COVID-19 in pediatric oncology from French pediatric oncology and hematology centers: high risk of severe forms. Pediatr Blood Cancer. 2020;67:e28392. https://doi.org/10.1002/pbc.28392.
8. Ai T, Yang Z, Hou H, Zhan C, Chen C, Lv W, et al. Correlation of chest CT and RT-PCR testing in coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. Radiology. 2020;296(2):E32–40. https://doi.org/10.1148/radiol.2020200642.
9. Kanellopoulos A, Ahmed MZ, Kishore B, Lovell R, Horgan C, Paneesha S, et al. COVID-19 in bone marrow transplant recipients: reflecting on a single-center experience. Br J Haematol. 2020;190:e57–94. https://doi.org/10.1111/bjh.16856.
10. Feldstein LR, Rose EB, Horwitz SM, Collins JP, Newhams MM, Son MBF, et al. Multisystem Inflammatory Syndrome in the U.S. Children and Adolescents. N Engl J Med. 2020;383:334–46. https://doi.org/10.1056/NEJMoa2021680.
11. Delavari S, Abolhassani H, Abolnezhadian F, Babaha F, Iranparast S, Ahanchian H, et al. Impact of SARS-CoV-2 Pandemic on Patients with Primary Immunodeficiency. J Clin Immunol. 2021;41(2):345–55. https://doi.org/10.1007/s10875-020-00928-x.