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LETTER TO THE EDITOR

Robust and sustained antibody response to SARS-CoV-2 in a child pre and post autologous hematopoietic stem cell transplant

To the Editor:

The coronavirus disease (COVID)-19 pandemic caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has been evolving rapidly, and till date has resulted in over a million deaths worldwide. Previous reports have suggested that the severity of the disease is mild and self-limiting upper respiratory tract infection in most children.[1] The characterization of COVID-19 in pediatric cancer and hematopoietic stem cell transplant (HSCT) patients is limited in the available literature. The effects of COVID-19 infection on the outcomes of HSCT in children are still being explored.

Children with malignancies and those post HSCT have persistent immune alterations even months after treatment completion. Low antibody concentrations have been demonstrated in a majority of patients, regardless of the malignancy and chemotherapy regimen.[2] This has compounded the uncertainties in the management of pediatric HSCT patients. The antibody response in the immunosuppressed population may not be robust, and delayed clearance of the live virus could be a problem. Uncertainty exists on when a child could be fit for intensive chemotherapy and HSCT after an infection with SARS-CoV-2. The European blood and marrow transplant (EBMT) society guidelines state that if a transplant candidate is diagnosed with COVID-19, a deferral of HSCT by at least 3 months is advisable.[3]

Here, we report the case of a child who was able to mount a good antibody response to the novel coronavirus despite being on chemotherapy in the recent past, and the response was sustained during and after his successful autologous HSCT.

A 3-year-old child with n-myc gene amplified, high-risk, stage-III, left-sided suprarenal neuroblastoma achieved complete remission after induction chemotherapy on the OPEC/OJEC protocol.[4] His autologous stem cells had been previously harvested and stored. Due to delay in admission for his autologous HSCT, caused because of the lockdown imposed during the COVID-19 pandemic, he received two extra cycles of irinotecan and temozolomide. Two months post his last chemotherapy cycle, he was taken up for consolidation with an autologous HSCT.

Before admission for HSCT, the child underwent a mandatory screening test for the SARS-CoV-2 and was found to be positive by the cartridge-based nucleic acid amplification test (CBNAAT). After 2 weeks of home isolation, during which time the child remained asymptomatic, the child tested negative by CBNAAT, on the 17th day. His total serum SARS-CoV-2 antibody titers (IgG and IgM), estimated using chemiluminescent immunoassay, were reactive with an index of >10 (>1 taken as reactive).

The child was started (6 days after testing negative) on his HSCT-conditioning regimen consisting of busulfan at a dose of 1 mg/kg intravenously every 6 h for 4 days (day −6 to day −3) and melphalan at a dose of 140 mg/m^2 intravenously on day −2.

He was infused his prestored stem cells on day 0, and the CD34+ cell dose given was 1×10^6/kg. Post his stem cell infusion, the child developed complications of mucositis, febrile neutropenia, and *Clostridium difficile* colitis, which were managed with supportive care and appropriate antibiotics. The child also developed rapid respiration, low-grade fever, and facial puffiness on day +16, which was attributed to engraftment syndrome. He received 3 days of low-dose oral steroids for the same. Neutrophil engraftment was achieved on day +18, and platelet engraftment occurred on day +24. His SARS-CoV-2 antibody titers that were repeated on day 0 and day +22 (ie, on the 37th and 55th day from initial positivity) were reactive, with titer indices being greater than 10 each time. The total leucocyte count (TLC) and absolute neutrophil count (ANC) in relation to the antibody titers are shown in Figure 1. The child was discharged after a successful HSCT.

The immune response to the SARS-CoV-2 infection is varied in different population groups. Children who are post chemotherapy and HSCT are immunosuppressed and are considered high-risk groups. Chemotherapy and HSCT, both allogeneic and autologous, cause defects in humoral and cell-mediated immunity. It is established that they have decreased antibody titers against common infections and vaccine-preventable diseases.[5] Hypogammaglobulinemia secondary to chemotherapy and HSCT is a common complication and is found more in younger children.[6]

Antibodies are important in defense against viruses. Virus-elicited antibodies provide lifelong surveillance and protection from future infections.[7] Imunoglobulin (Ig) M and IgG antibodies to SARS-CoV-2 develop between the first and second week of infection in most cases. In mild cases, the antibody response may take longer and in a minority the antibodies may not be detected at all. The detection of antibodies to SARS-CoV-2 does not indicate directly protective immunity parameters for protection are yet unestablished.[8] Unlike the experience in the SARS-CoV-1 infection where about half of the patients had detectable IgG antibodies even after 3 years of infection,[9] the duration and effectiveness of antibody response to SARS-CoV-2 remains unestablished.

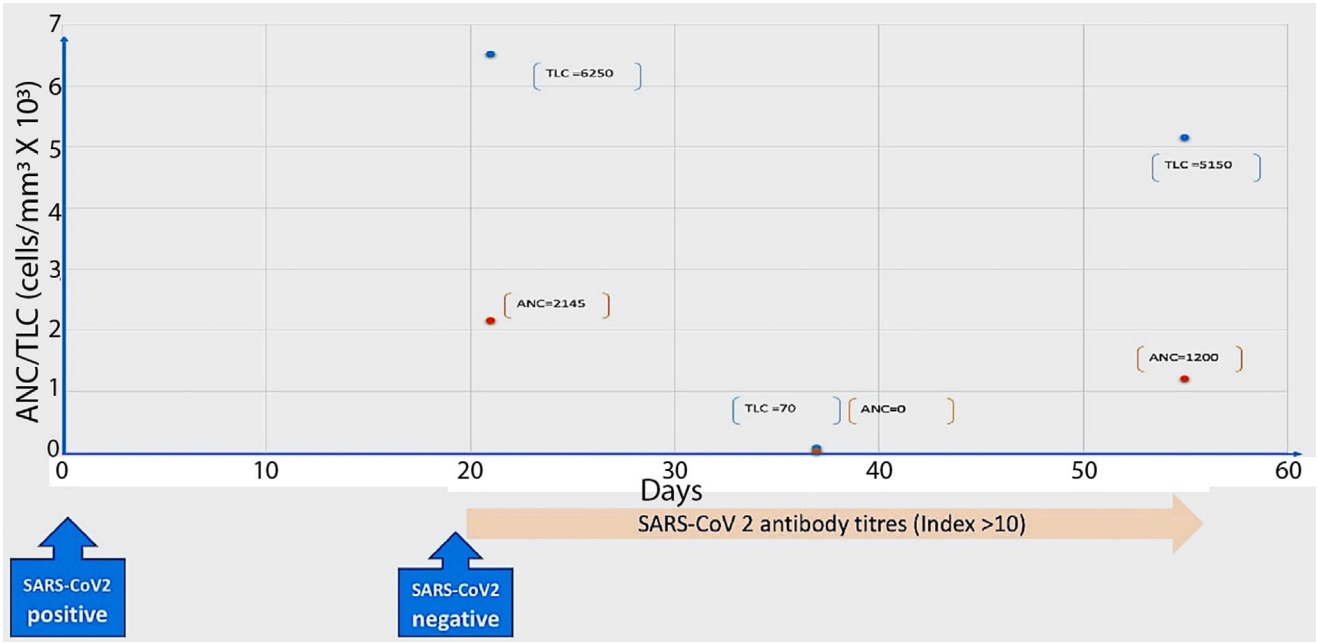

FIGURE 1 Time course of leukocyte counts. Day 0 is the day of initial SARS-CoV-2 positivity. Hematopoietic stem cell transplant was performed on day 24. ANC, absolute neutrophil count; TLC, total leukocyte count; SARS-CoV2, severe acute respiratory syndrome coronavirus-2; HSCT, hematopoietic stem cell transplant

Most of the reports of COVID-19 in the setting of HSCT have been in the context of post-HSCT infection. Haroon et al reported 11 patients who had undergone HSCT, and acquired the SARS-CoV-2 infection in the range of day +5 to 192 months post-HSCT. All the patients had mild disease and had good outcomes.[10] Similarly, Vincent et al reported the outcomes of eight children with a median age of 10 years who had undergone HSCT. Two patients required intensive care and one patient died due to alveolar hemorrhage. Coronavirus polymerase chain reaction (PCR) became negative in a mean time of 20 days in six patients (75%), one patient with immunodeficiency was persistently positive, and the patient who died had a positive PCR.[11] The EMBT recommendations (updated in November 2020) in view of the COVID-19 pandemic state that the decision to proceed for HSCT after the diagnosis of COVID-19 should take into account the risk of the patient associated with on one hand the delay of the procedure and on the other proceeding with conditioning. It is mentioned that in general if a transplant candidate is diagnosed with COVID-19, a deferral of at least 3 months is advisable. However, this may not always be possible due to the risk for progression of the underlying disease.[3]

In our report, we demonstrate that this child on chemotherapy for a high-risk malignancy was able to mount a robust immune response against the SARS-CoV-2 virus and cleared the virus during his period of home isolation. Further, humoral immunity, reflected by the total immunoglobulin levels against the virus, was achieved and sustained at good levels during and after the HSCT.

Few pediatric patients post chemotherapy may be capable of mounting a good antibody response to the SARS-CoV-2 virus after infection. The antibody response helps in clearance of the virus, and facilitates the child in proceeding for HSCT and intensive chemotherapy. As seen in our patient, in some children this response could be sustained at good levels even after potentially immunosuppressive HSCT. Estimation of antibody levels and its correlation with viral clearance in a prospective manner may further help us formulate guidelines that may be more generalizable.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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REFERENCES

1. Castagnoli R, Votto M, Licari A, et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in children and adolescents: a systematic review. *JAMA Pediatr*. 2020;174(9): 882-889.
2. Mustafa MM, Buchanan GR, Winick NJ, et al. Immune recovery in children with malignancy after cessation of chemotherapy. *J Pediatr Hematol Oncol*. 1998;20(5):451-457.
3. Ljungman P, Mikulska M, de la Camara R, et al. The challenge of COVID-19 and hematopoietic cell transplantation; EBMT recommendations for management of hematopoietic cell transplant recipients, their donors, and patients undergoing CAR T-cell therapy. *Bone Marrow Transplant*. 2020;55:2071-2076.
4. Tweddle DA, Pinkerton CR, Lewis IJ, Ellershaw C, Cole M, Pearson AD. OPEC/OJEC for stage 4 neuroblastoma in children over 1 year of age. *Med Pediatr Oncol*. 2001;36(1):239-242.
5. Ljungman P, Cordonnier C, Einsele H, et al. Vaccination of hematopoietic cell transplant recipients. *Bone Marrow Transplant*. 2009;44: 521.
6. Frangoul H, Min E, Lu Z, et al. Incidence and risk factors for hypogammaglobulinemia in pediatric allogeneic stem cell transplant (SCT) patients. *Blood*. 2012;120(21):4492.
7. Murin CD, Wilson IA, Ward AB. Antibody responses to viral infections: a structural perspective across three different enveloped viruses. *Nat Microbiol*. 2019;4(5):734-747.
8. Zhao J, Yuan Q, Wang H, et al. Antibody responses to SARS-CoV-2 in patients of novel coronavirus disease 2019. *medRxiv*. 2020. https://doi.org/10.1101/2020.03.02.20030189
9. Wu LP, Wang NC, Chang YH, et al. Duration of antibody responses after severe acute respiratory syndrome. *Emerg Infect Dis*. 2007;13(10):1562-1564.
10. Haroon A, Alnassani M, Aljurf M, et al. COVID-19 post hematopoietic cell transplant, a report of 11 cases from a single center. *Mediterr J Hematol Infect Dis*. 2020;12(1):e2020070.
11. Vicent MG, Martinez AP, Trabazo Del Castillo M, et al. COVID-19 in pediatric hematopoietic stem cell transplantation: the experience of Spanish Group of Transplant (GETMON/GETH). *Pediatr Blood Cancer*. 2020;67(9):e28514.