Acute Exacerbation of Graft-versus-Host Disease following SARS-CoV2 infection after Hematopoietic Stem Cell Transplant in Two Pediatric Patients

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Letter to the Editor: Interesting clinical observation

Title: Acute Exacerbation of Graft-versus-Host Disease following SARS-CoV2 infection after Hematopoietic Stem Cell Transplant in Two Pediatric Patients

Running Title: Graft-versus-Host Disease and SARS-CoV2 infection

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Abbreviations key:

HSCT	Hematopoietic stem cell transplant
GVHD	Graft-versus-host disease
HLA	Human leukocyte antigen
COG	Children's Oncology Group
ALL	Acute lymphoblastic leukemia
CMML	Chronic myelomonocytic leukemia
MRD	Matched related donor

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To the Editor:

Graft-versus-host disease (GVHD) is a significant cause of morbidity and mortality in patients receiving hematopoietic stem cell transplant (HSCT), with a reported mortality rate as high as 50% in patients with grade 3-4 GVHD.[1] The complex pathophysiology of GVHD involves donor T cell activation and cytotoxicity against inflamed host tissue.[1,2] There are many known risk factors such as Human Leukocyte Antigen (HLA) mismatch, high cell dose, and history of total body irradiation[1,3] Infectious triggers, such as human herpesvirus-6 (HHV-6) and CMV reactivation are also well-reported in literature, although the underlying mechanism is not elucidated.[4,5,6,7] The authors share two pediatric cases of acute GVHD exacerbation after SARS-CoV2 infection during the post-transplant period. To date, there is limited literature regarding sequelae of SARS-CoV2 infection in pediatric patients after HSCT.[8,9,10,11,12] We aim to bring to light that SARS-CoV2 infection (without COVID-19 disease) may be a potential trigger for acute GVHD exacerbation.

Case #1:

Patient 1 is a 13-year-old male with history of very-high-risk refractory Philadelphia-like B-cell acute lymphoblastic leukemia (ALL) for which he received a haploidentical bone marrow transplant after achieving complete remission one month prior to transplant. His conditioning regimen consisted of fludarabine, total body irradiation, and post-transplant cyclophosphamide. He engrafted sixteen days after stem cell infusion, with negative MRD on bone marrow studies on day +30 and day +100. The patient's GVHD prophylaxis included post-transplant cyclophosphamide, mycophenolate mofetil, and tacrolimus. Soon after engraftment, the patient developed grade 1 gut GVHD, which improved with steroids and a single dose of basiliximab. Oral steroids were successfully weaned off and the patient had a stable post-transplant course with resolution of GI symptoms. On day +122, the patient tested positive for SARS-CoV2 by RT-PCR of a nasopharyngeal swab, which was obtained for pre-procedural screening. He remained asymptomatic and subsequently did not receive any viral-directed therapy for immediate sequelae of SARS-CoV2 infection.

However, about one month after testing positive for SARS-CoV2, the patient developed worsening rash and diarrhea as well as hematochezia. A full infectious workup was negative. Elevated biomarkers (ST2, Reg3α) from an acute GVHD panel supported clinical diagnosis of late onset, grade 4, acute lower gastrointestinal GVHD. He received IV methylprednisolone, other immunomodulatory agents, as well as extracorporeal photopheresis (ECP) for treatment of GI GVHD. Unfortunately, he proceeded to develop GVHD of his liver, confirmed by biopsy two months after onset of hyperbilirubinemia. By time of this publication, this patient has passed away due to complications secondary to GVHD.

Case #2:

Patient 2 is a 16-year-old female with history of treatment-associated chronic myelomonocytic leukemia (CMML) that developed three years after completing treatment for pre-B lymphoblastic lymphoma. The patient received a matched related donor (MRD) bone marrow transplant after completing myeloablative conditioning regimen consisting of busulfan and cyclophosphamide. She engrafted seventeen days after stem cell infusion. GVHD prophylaxis consisted of tacrolimus and methotrexate. There was no concern for acute GVHD immediately after transplant. However, the patient's course was complicated by positive SARS-CoV2 detected by RT-PCR on pre-procedural surveillance nasopharyngeal swab obtained 34 days post-transplant. Although the patient was asymptomatic, she was treated with bamlanivimab (a monoclonal antibody for treatment of COVID-19) due to her proximity from transplant. About three weeks after testing positive for SARS-CoV2, the patient was noted to have exam findings concerning for GVHD of her skin and upper GI tract, as well as elevation in transaminases. She subsequently underwent a liver biopsy which confirmed grade 2 GVHD of her liver. The patient was treated with steroids as well as other immunomodulatory medications, with which symptoms of GVHD improved. She is currently tolerating a wean in immunosuppression without recurrence of her transaminitis.

Given the severity of symptoms and impact on long-term survival and quality of life, it is important to recognize risk factors for early recognition and treatment of GVHD. For known viral triggers such as HHV-6 and CMV, patients are often started on prophylactic anti-viral medication and monitored closely for viral reactivation. SARS-CoV2 is a novel coronavirus that has rapidly spread across the world. To date, there is no literature available describing long-term sequelae of SARS-CoV2 infection in pediatric patients who have received HSCT. We wanted to recognize the association observed in two cases of acute GVHD exacerbation in patients who tested positive for SARS-CoV2 after HSCT. Furthermore, we note that the second patient received SARS-CoV2-directed therapy, after which she experienced a less severe course of GVHD. Meanwhile, the first patient did not receive directed therapy and subsequently required prolonged hospitalization to treat acute exacerbation of skin and lower GI GVHD, as well as new onset liver GVHD. He required use of multiple immunomodulatory agents in addition to photopheresis and systemic corticosteroid therapy prior to his untimely death.

The authors recognize that there are many confounding factors that played a role in these two patients' clinical course. Namely, the source of HSCT- patient 1 received a haploidentical transplant while patient 2 received a MRD product. Historically, the incidence of grade II-IV acute GVHD is lower in patients who received MRD HSCT compared to those who received haploidentical HSCT (25-27% vs 20-80%).[3,13]However, recent data published since the development of post-transplant cyclophosphamide regimens have shown a comparable incidence of grade III-IV acute GVHD between the two groups (9.8 – 11% in MRD vs 0-11% in haploidentical transplant).[14,15.16,17] The authors recognize that there have been no head-to-head prospective studies in pediatrics comparing GVHD incidence for MRD HSCT and haploidentical HSCT with post-transplant cyclophosphamide. Therefore, it is difficult to conclude whether the second patient's lower baseline risk of GVHD or use of SARS-CoV2 directed therapy contributed to the less severe course of GVHD.

This possible association between SARS-CoV2 and development of severe GVHD warrants further studies to identify long-term sequelae of SARS-CoV2. If a strong correlation between SARS-CoV2 infection and acute exacerbation or onset of GVHD is found, it may be beneficial for post-transplant patients (symptomatic or not) to receive SARS-CoV2-directed therapy to alleviate risk of steroid-refractory GVHD.

Conflict of Interest: The authors do not have any conflicts of interest to disclose.

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