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LETTER TO THE EDITOR

Acute exacerbation of graft-versus-host disease following SARS-CoV2 infection after hematopoietic stem cell transplant in two pediatric patients

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[1,3] including infectious triggers such as human herpesvirus-6 (HHV-6) and cytomegalovirus (CMV) reactivation.[4–7] The authors share two pediatric cases of acute GVHD exacerbation after SARS-CoV2 infection during the posttransplant period. To date, there is limited literature regarding long-term sequelae of SARS-CoV2 in patients after HSCT.[8–12] 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 recurrent Philadelphia-like B-cell acute lymphoblastic leukemia for which he received a haploidentical bone marrow transplant. Conditioning regimen consisted of fludarabine and total body irradiation. GVHD prophylaxis included post-transplant cyclophosphamide (PT-Cy), mycophenolate mofetil, and tacrolimus. Engraftment occurred 16 days after stem cell infusion, at which time the patient developed diarrhea. Infectious workup was negative, and symptoms improved after a single dose of basiliximab and 3 days of IV steroids. Subsequently, oral steroids were successfully weaned off over 3 months as his gastrointestinal (GI) symptoms resolved, and the patient was clinically diagnosed with stage 1 gut GVHD.

On day +122, the patient tested positive for SARS-CoV2 by RT-PCR obtained for screening. He remained asymptomatic and subsequently did not receive any viral-directed therapy. However, about 1 month afterwards, 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, stage 4, grade 4, acute lower gastrointestinal GVHD. Biopsy was not pursued given his tenuous clinical status. He received IV methylprednisolone, other immunomodulatory agents, as well as extracorporeal photopheresis (ECP) for treatment of GI GVHD. Unfortunately, he proceeded to develop liver GVHD, confirmed by biopsy, 2 months after onset of hyperbilirubinemia. By time of this publication, this patient 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 that developed 3 years after completing treatment for pre-B lymphoblastic lymphoma. The patient received a matched-related donor (MRD) bone marrow transplant after myeloablative conditioning with busulfan and cyclophosphamide. She engrafted 17 days after stem cell infusion. GVHD prophylaxis consisted of tacrolimus and methotrexate. There was no immediate concern for acute GVHD after transplant. However, the patient's course was complicated by positive SARS-CoV2 detected by surveillance RT-PCR obtained 34 days post-transplant. Given her proximity from transplant, the patient was treated with bamlanivimab (a monoclonal antibody for treatment of COVID-19) despite being asymptomatic. After approximately 3 weeks, the patient was noted to have exam findings concerning for GVHD of her skin and upper GI tract, as well as elevated transaminases. She subsequently underwent a liver biopsy which confirmed stage 1, grade 2 GVHD. The patient was treated with steroids as well as other immunomodulatory medications, with which symptoms improved. She is currently tolerating a wean in immunosuppression without recurrence of her transaminitis.

Given the 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 therapy and closely monitored 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 after HSCT. We hope to recognize a possible association observed in two cases of acute GVHD exacerbation in patients who tested positive for SARS-CoV2 after HSCT. Furthermore, we note that patient 2 experienced a less severe course of GVH after receiving SARS-CoV2-directed therapy. In contrast, patient 1 did not receive SARS-CoV2-directed therapy and developed severe acute exacerbation of skin and lower GI GVHD, as well as new onset liver GVHD 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 an 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 PT-Cy

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).[14–17] 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 PT-Cy. Therefore, it is difficult to conclude whether lower baseline risk of GVHD or use of SARS-CoV2-directed therapy in patient 2 contributed to a 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 declare that there is no conflict of interest.

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