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

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Abstract

The novel coronavirus, SARS-CoV2 has affected over 28 million people in the United States as of February 2021.1 Limited literature describe the effects of SARS-CoV2 infection on pediatric patients who have received hematopoietic stem cell transplant (HSCT). Graft-versus-host disease (GVHD) is a significant cause of morbidity and mortality in post-transplant patients. Although the pathophysiology of GVHD is well-described; identification of risk factors and successful treatment of severe, refractory GVHD is still wanting. We present two pediatric cases of acute GVHD exacerbation after SARS-CoV2 infection to recognize a potential risk factor for development of GVHD in pediatric HSCT recipients.

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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: Minimal residual disease

- CAR: Chimeric antigen receptor

- FISH: Fluorescence in situ hybridization

Declaration of Interest: None

Abstract:

The novel coronavirus, SARS-CoV2 has affected over 28 million people in the United States as of February 2021.[1] Limited literature describe the effects of SARS-CoV2 infection on pediatric patients who have received hematopoietic stem cell transplant (HSCT). Graft-versus-host disease (GVHD) is a significant cause of morbidity and mortality in post-transplant patients. Although the pathophysiology of GVHD is well-described; identification of risk factors and successful treatment of severe, refractory GVHD is still wanting. We present two pediatric cases of acute GVHD exacerbation after SARS-CoV2 infection to recognize a potential risk factor for development of GVHD in pediatric HSCT recipients.

Introduction:

Graft-versus-host disease (GVHD) is a significant cause of morbidity and mortality in patients receiving hematopoietic stem cell transplant (HSCT). It is estimated that about 50% of patients who undergo HSCT develop some grade of GVHD,[2] and patients with grade 3-4 GVHD have mortality rates reported as high as 50%. The pathophysiology behind GVHD is complex but can be described in three main steps. The first step involves damage to the host tissue resulting in production of pro-inflammatory cytokines. This activates the host antigen presenting cells (APC), which in turn leads to activation of donor T cells. Finally, cellular cytotoxicity and destruction of host target tissue occurs, while the host is unable to mount a response against the activated donor T cells.[2,3]Corticosteroids are the first line therapy used to treat GVHD. However, many patients are refractory to steroid therapy and there is no consensus on second line therapies in pediatric patients.[2] This makes severe cases of GVHD difficult to treat and contributes to the high rate of morbidity and mortality.

There are many risk factors for developing GVHD including infectious triggers.[2,4] Human herpesvirus-6 (HHV-6) and CMV reactivation are most notably reported to increase risk of GVHD.[5,6,7,8,9,10] [11,12,13,14] The underlying mechanism explaining this relationship is not elucidated, though is likely related to how the infectious agent affects the donor's T cell response and activation in the host.[6]

We observed two pediatric cases of acute exacerbation of GVHD 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[15,16,17,18,19,20,21,22,23] and no reports of the effects on GVHD after infection. We hope to recognize SARS-CoV2 infection (without COVID-19 disease) as a potential trigger for acute GVHD exacerbation.

Methods:

We reviewed two cases of patients who received bone marrow transplantation at Texas Children's Hospital and developed GVHD after SARS-CoV2 infection.

Results:

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). He was referred for bone marrow transplant due to refractory disease with 25.2% blasts reported in bone marrow studies at the end of interim maintenance according to the Children's Oncology Group (COG) protocol AALL1131. The patient achieved complete remission with negative minimal residual disease after receiving CD19-specific chimeric antigen receptor (CAR) T cells as a bridge to transplant. He was then conditioned with fludarabine, total body irradiation, and post-transplant cyclophosphamide in order to receive a haploidentical bone marrow transplant from his mother. He engrafted sixteen days after stem cell infusion, with negative MRD on bone marrow studies from 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 GVHD of the gut, for which he received IV methylprednisolone 1 mg/kg/day and a single dose of basiliximab. He was discharged home with oral prednisone after significant improvement on three days of IV steroids. Steroids were weaned off as an outpatient, with resolution of GI symptoms, until 122 days post-transplant. At that time, he became positive for SARS-CoV2 by RT-PCR, which was obtained prior to scheduled line removal. The patient remained asymptomatic and did not require hospitalization or 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. With onset of hematochezia, he was diagnosed with late onset, grade 4, acute lower gastrointestinal GVHD. He then had a prolonged hospitalization, during which he received methylprednisolone and other immunomodulatory agents. He was able to be discharged and continued GVHD management with twice weekly extracorporeal photopheresis (ECP), as well as multiple immunomodulatory drugs. No other viral infections or GVHD triggers were identified during this time period. Despite continued therapy, he developed GVHD of his liver (Fig. 1), which was confirmed by biopsy about 13 months post-transplant and unfortunately at the time of publication, patient has passed away due to complications secondary to GVHD.

Case #2:

Patient 2 is a 16-year-old female with history of chronic myelomonocytic leukemia (CMML) that developed three years after completing treatment for pre-B lymphoblastic lymphoma. This patient received a matched related bone marrow transplant from her brother due to persistent monosomy 7 on fluorescence in situ hybridization (FISH). Her myeloablative conditioning regiment consisted of busulfan and cyclophosphamide. She engrafted seventeen days after stem cell infusion.

The patient received tacrolimus and methotrexate as GVHD prophylaxis. 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, 34 days post-transplant. The patient was otherwise asymptomatic. Due to her close proximity to transplant at the time of this positive test, she was treated with a dose of bamlanivimab, a monoclonal antibody for the treatment of mild to moderate COVID-19 in patients at high risk for progressing to severe COVID-19. The patient remained asymptomatic and did not require hospitalization.

About three weeks after testing positive for SARS-CoV2, the patient was noted to have exam findings concerning for skin and upper GI GVHD, as well as elevation in transaminases (Fig 2) . She subsequently underwent a liver biopsy which confirmed grade 2 GVHD of her liver. She 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 transaminitis.

Discussion:

GVHD is a major cause of morbidity and mortality in patients after HSCT. Manifestations range from acute

onset of skin, gastrointestinal, and hepatic symptoms to chronic syndromes that can affect nearly every organ system.[24] Although there is agreement in utilization of corticosteroids as first-line therapy for GVHD, there is no consensus on treatment of steroid-refractory cases.[2] Given the severity of symptoms, impact on long-term survival and quality of life, and clinical presentation that is consistent with many other post-transplant complications, it is important to be able to recognize risk factors and hopefully diagnose and treat GVHD earlier in its course.

Potential triggers for acute GVHD are viral infections such as HHV-6 and CMV. With known viral triggers, patients are often started on prophylactic anti-viral medication and monitored closely. SARS-CoV2 is a novel coronavirus that has rapidly spread across the world. To date, there is no literature describing long-term sequelae of SARS-CoV2 infection in pediatric patients who have received HSCT. We present two cases of acute exacerbation of GVHD in patients who tested positive for SARS-CoV2 after HSCT. We hypothesize that SARS-CoV2 may serve as a trigger for GVHD. Furthermore, we note that patient 2 received SARS-CoV2-directed therapy, after which we observed a less severe course of GVHD that to date is controlled with oral corticosteroids and a calcineurin inhibitor. Meanwhile, patient 1 did not receive directed therapy after which he required prolonged hospitalization to treat acute exacerbation of lower GI GVHD in addition to skin GVHD. He also subsequently developed liver GVHD requiring biweekly photopheresis, and prolonged use of immunomodulatory agents and systemic corticosteroids prior to his passing.

Further studies to identify long-term sequelae of SARS-CoV2 are warranted, and 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 to receive SARS-CoV2-directed therapy even when asymptomatic or with mild symptoms.

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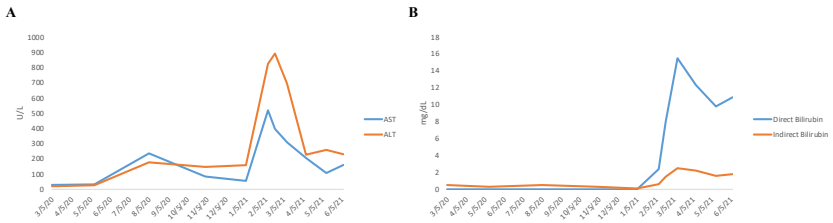
Legend:

FIGURE 1: (A) Liver transaminase and (B) direct and indirect bilirubin trend for Case 1- Patient underwent hematopoietic stem cell transplantation on 3/5/2020. He was positive for SARS-CoV2 by RT-PCR on 7/5/2020. On 8/14/2020, he was admitted for acute exacerbation of GI GVHD, followed by development of liver GVHD confirmed by biopsy on 4/14/2021.

FIGURE 2: Liver transaminase trend for Case 2- Patient underwent hematopoietic stem cell transplantation on 11/20/2020, followed by positive SARS-CoV2 by RT-PCR on 12/24/2020. She received bamlanivimab on 12/28/2020. On 1/19/2021, biopsy confirmed liver GVHD.



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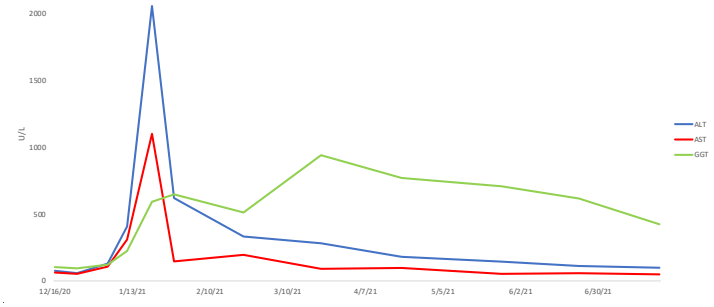

FIGURE 2: Liver transaminase trend for Case 2- Patient underwent hematopoietic stem cell transplantation on 11/20/2020, followed by positive SARS-CoV2 by RT-PCR on 12/24/2020. She received bamlanivimab on 12/28/2020. On 1/19/2021, biopsy confirmed liver GVHD.