ACUTE GVHD TRIGGERED BY COVID-19 IN A BONE MARROW RECIPIENT

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Abstract

Introduction There are few reports regarding risk of COVID-19-associated complications in bone marrow recipients. We report a patient who had graft-versus-host disease triggered by COVID-19. Results The patient was a 17-year-old boy who underwent HSCT from matched sibling donor for CML. He had complete donor chimerism at day +30. Cyclosporine was tapered and stopped at day +65. Until day +93, he had no complaints. The patient started to suffer from cutaneus and gastro-intestinal grade III GVHD after the diagnossis of CIVID-19. Discussion In the absence of any other condition to explain this clinical picture and the good response to GVHD treatment indicate that the triggering factor in the development of GVHD may be COVID-19 in the era of TLR, which plays a common role in the pathogenesis of both GVHD and COVID-19.

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* **Key words:** Bone marrow transplantation, children, COVID-19, GVHD

Abbreviations Key

SARS-CoV-2A	Severe acute respiratory syndrome coronavirus 2
HSCT	hematopoietic stem cell transplant
GVHD	graft-versus-host disease
RT-PCR	polymerase chain reaction
TLRs	Toll-like receptors
TNF	tumor necrosis factor
IFN	interferon
IL	interleukin

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Introduction

The COVID-19 pandemic caused by 'Severe acute respiratory syndrome coronavirus 2' (SARS-CoV-2A) was first described at the end of 2019 and have spread all over the world. Although elderly and people with comorbidities are the most affected by the severe manifestations of the disease, COVID-19 seems to affect children to a lesser degree.[1] Data concerning the impact of COVID-19 on hematopoietic stem cell transplant (HSCT) patients are scarce and variable. There are few reports – mostly from adults- regarding risk of COVID-19-associated complications secondary to immunosuppressive therapy or delayed immune reconstitution at the post-transplant period.[2] However, little is known about children and adolescents with HSCT. Here, we report an adolescent patient who was diagnosed with COVID-19 after hematopoietic stem cell transplantation and had graft-versus-host disease (GVHD) triggered by COVID-19.

Results

The patient was a 17-year-old boy who underwent HSCT from matched sibling donor with peripheral blood stem cells in Behcet Uz Children's Hospital, Turkey on August 18, 2020 for chronic myeloid leukemia. The conditioning regimen was busulfan plus cyclophosphamide; single agent cyclosporine was introduced for GVHD prophylaxis. No notable event like acute GVHD, sepsis, veno-occlusive disease or infection during early HSCT period was recognized. He had neutrophil engraftment on day +17 and platelet engraftment on day +23. Bone marrow aspirations (first and second months after HSCT) showed cytological and molecular remission and complete donor chimerism. As he had no GVHD, cyclosporine was tapered and stopped at day +65. Until day +93, he had no complaints during clinical visits and he had complete donor chimerism. At day +94, his mother showed fever, anosmia, chest pain and shortness of breath. Real-time reverse transcriptase polymerase chain reaction (RT-PCR) testing for SARS-CoV-2 was positive on nasopharyngeal swab specimen. His mother hospitalized with pneumonia and shortness of breath. The patient was quarantined at home without any symptoms regarding COVID-19. Three days after this event, the patient started to suffer from large amount of watery diarrhea - three to five times a day with no blood - and abdominal pain, nausea, vomiting, and anorexia. One day later, the patient presented a maculopapular rash initially involving the nape of the neck, ears, shoulders, the palms of the hands, and the soles of the feet. It was pruritic. When he was admitted to the hospital, he had maculopapular rash <25 percent of body area, large amount of watery diarrhea, abdominal pain, nausea, vomiting, and anorexia but he had no fever or respiratory signs. The. radiological imaging revealed no finding related to COVID infection but RT-PCR testing for SARS-CoV-2 was positive on nasopharyngeal swab specimens.. No other viral reactivation or infection (cytomegalovirus, Epstein-Barr virus, adenovirus), as well as pathogens in the gaita specimen was detected. At that time, the patient was still on preventive anti-infectious treatment by sulfamethoxazole-trimethoprime, fluconazole, and acyclovir. But a period of one month had passed since cyclosporine was stopped. Complete blood count showed 3.5 × 109/L white blood cells including 2.2 × 109/L neutrophils, and lymphopenia (0.43 × 109/L), hemoglobin 9.6 g/dl, and platelets 103 × 109/L. Blood chemistry showed electrolyte imbalances and elevated kidney function tests. But liver function tests and bilirubines were in normal limits. He had metabolic acidosis in blood gas. Emprically metronidasole for diarrhea and favipravir for COVID-19 were started. The patient received intravenous immunoglobulin for immune deficiency secondary to HSCT. After two days, the rash spread to involve the whole integument, eventually become confluent one day after. He had still large amount of watery diarrhea with 10 to 15 times a day, abdominal pain, nausea, vomiting, and anorexia but no fever or respiratory signs. Cyclosporine IV and steroid 2 mg/kg was started because of the cutaneous and digestive GVHD grade III. Endoscopic evaluation of gastrointestinal tract could not be done because of the diagnosis of COVID. At day 5 after starting steroid and cyclosporine, the clinic picture was improved. At day 7, he had rash 25 to 50 percent of body area, diarrhea less watery with 5 to 10 times a day. He had no anorexia, food intolerance, nausea, and vomiting. We added non-absorbable budesonide and mycophenolate mophetil PO to the treatment. At day 14, he had rash <25 percent of body area, diarrhea less watery with 2 to 4 times a day. His COVID-19 PCR test was still positive. In the following period, we tapered the steroid dose. At day 29, his COVID-19 PCR test was negative in the wo samples taken 24 hours apart after the initial positive test. IgG antibody was still negative on day 35 after the initial COVID-19 PCR positivity.

Discussion

Pediatric cases represent 1-5% of COVID-19 cases worldwide and there is a paucity of data on COVID-19 impact on bone marrow transplant patients. Children are less infected perhaps due to the lower expression level of angiotensin-converting enzyme 2 in their nasal mucosa.[3] Bone marrow recipients are suspected to be more prone to COVID-19 as they have immunosuppressive therapy or delayed immune reconstitution after transplantation. Reports describing the COVID infections so far in bone marrow transplant recipients always have pointed these two situations. Most of the COVID cases in these reports were on immunosuppressive treatments or there was a history of high dose steroid use due to GVHD. In our case, the immunosuppression treatment was discontinued approximately one month before the diagnosis of COVID-19 and there was no sign of GVHD, both in the early post-transplant period and the time around the COVID-19 diagnosis. We know that, in most recipients, the first clinical manifestation of acute GVHD usually occurs at or near the

time of the white blood cell engraftment, not at around day 100. In our opinion, COVID-19 infection was the factor that triggered GVHD findings after the COVID infection had transmitted from his mother.

Pathologically, acute GVHD is apparent as an inflammatory T cell infiltrate with associated tissue destruction and apoptosis. Many factors contribute to the pathophysiology of acute GVHD.[4,5] In acute GVHD, a trigger initiates inflammation mediated by the innate immune system in cooperation with T and B lymphocytes of the adaptive immune system.[6]Macrophages, neutrophils, and dendritic cells mediate this response through Toll-like receptors (TLRs), which are involved in pathogen recognition.[7-9] And in the end, TLR pathway activation induces transcriptional activation of interferon (IFN) alpha and induces tumor necrosis factor (TNF) and interleukin (IL)-6.[10-12] IFN alpha drives Th1 commitment and results in IFN gamma production and, together, IFN alpha and IFN gamma induce chemokines that recruit Th1 cells to sites of inflammation and enhance processing and presentation of host antigens.[6,13] These interactions shows that TLRs are important contributing factors to the pathogenesis of acute GVHD.

Several clinical variables are associated with the development of GVHD such as donor type, source, sex-mismatch and infection history (eg, CMV, EBV).[6] Like EBV and CMV, COVID-19 which is a powerful trigger for immune response may have a potential to trigger viral-mediated TLR4 activation.

From the studies referring the pathophysiology of COVID, we have learned that TLRs play a significant role between COVID and exacerbated immunological host response leading a cytokine storm. Overexpression of pro-inflammatory cytokines such as IL-6 and TNF alpha, which are products of the TLR4 pathway, may play a critical role as a trigger for acute GVHD as SARSCoV-2 spike protein has strong interaction with TLRs. This may be the link between the unbalanced immune response in COVID-19 and GVHD.[14]

In conclusion, although the diagnosis of GVHD was not histologically proven in this patient, the patient's clinic, the absence of any other condition to explain this clinical picture and the good response to GVHD treatment indicate that the triggering factor in the development of GVHD may be COVID-19 in the era of TLR, which plays a common role in the pathogenesis of both GVHD and COVID-19. So, it should be kept in mind that COVID-19 may not be so innocent as reported in children and especially in the patients with HSCT and may progress with manifestations other than classical findings in bone marrow transplant recipients.

* No conflict of interest

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