COVID-19 Infection and Primary Graft Failure in a Pediatric Hematopoietic Stem Cell Transplant Patient

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Abstract

Currently, data on the effects of the novel Coronavirus disease (COVID-19) on hematopoietic stem cell transplant (HSCT) recipients is limited. In this case, an 8-year-old male with IPEX syndrome underwent allogeneic HSCT and was found COVID-19 positive 23 days post-transplant. He was treated with a 10-day course of remdesivir, three doses of tocilizumab, and two units of COVID-19 convalescent plasma (CCP). Initially, inflammatory markers decreased with treatment. However, he experienced primary graft failure, most likely secondary to COVID-19 infection, developed multiple systemic infections, and subsequently died before a second graft infusion could be administered.

Introduction

December 2019 marked the emergence of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), leading to the COVID-19 pandemic. As of May 2020, the World Health Organization (WHO) has reported over 4.7 million confirmed cases with more than 315,000 deaths worldwide.[1] In the United States, the Center for Diseases Control and Prevention (CDC) has confirmed more than 1.4 million cases with over 80,000 deaths; more than 35,000 cases are in the pediatric population.[2] Several treatment approaches are being studied, and approved therapies are emerging.

Remdesivir is an investigational nucleotide analog that causes premature termination of viral RNA transcription, targeting viral RNA-dependent RNA polymerase.[3] A large case series by Gilead Scientific showed improvement in respiratory support and overall mortality of patients treated for COVID-19 with remdesivir.[4] In May 2020, the U.S. Food and Drug Administration (FDA) approved the use of remdesivir for the treatment of suspected or laboratory-confirmed COVID-19 infection in adults and children hospitalized with severe disease based on clinical trials showing a shortened recovery time in patients treated with remdesivir.[5]

The SARS-CoV-2 virus is thought to cause a hyperinflammatory state similar to that seen in cytokine release syndrome (CRS) due to the dramatic rise in inflammatory markers. Symptomatology in such cases includes cough, tachypnea, and hypoxia and can progress to hypotension, acute respiratory distress syndrome, and other end-organ damage. In COVID-19 hospitalized patients, evidence shows an increase in inflammatory markers and cytokines, especially Interleukin-6 (IL-6), which is transiently produced in response to infections and tissue injuries, and contributes to host defense by stimulating acute phase responses and immune reactions.[6] Tocilizumab is a humanized anti-IL-6 receptor antibody that reduces the effect of IL-6 secretion during cytokine release syndrome (CRS). A systematic review reported recovery in 75% of patients with COVID-19-related CRS treated with tocilizumab.[7]

COVID-19 convalescent plasma (CCP) is another proposed treatment based on the creation of neutralizing antibodies after exposure to an illness. The FDA suggests that the use of CCP from recovered COVID-19

patients can be used for the treatment of COVID-19 infection.[8]A systematic review indicates that CCP limits viral reproduction in the acute phase of infection, hastening a rapid recovery.[9]

Thus far, data suggest that the majority of children with COVID-19 experience a mild, self-limited illness. We present the clinical course of a severely immunocompromised patient who contracted SARS-CoV-2 during the peri-engraftment period following an allogeneic HSCT and subsequently developed primary graft failure.

Case Report

An 8-year-old African-American male with immune-dysregulation polyendocrinopathy X-linked (IPEX) syndrome underwent haploidentical, related bone marrow HSCT. The conditioning regimen included busulfan, fludarabine, rabbit anti-thymoglobulin, and post-transplant cyclophosphamide. Prophylaxis for graft versus host disease (GVHD) included mycophenolate mofetil and cyclosporine.

On Day+21 post-transplant, he developed fever without associated symptoms, prompting infectious workup. Due to lack of engraftment, a sedated bone marrow aspiration was planned 2 days later; prior to sedation he tested positive for COVID-19 via nucleic acid amplification testing. He began experiencing mild respiratory distress, and a chest CT showed bilateral scattered central and peripheral ground-glass opacities (Picture 1). Remdesivir was approved for compassionate use through Gilead Scientific, and a 10-day course treatment began on day +26. Shortly after starting treatment, he required transfer to PICU for non-invasive ventilation due to respiratory distress.

Inflammatory parameters were measured daily (Table 1). We based our clinical decision for treatment calculating an HScore[10] of 209, which correlated with a 92.8% risk probability of CRS, so he was treated with two doses of tocilizumab and one unit of CCP. With these interventions, his fevers resolved but his neutropenia persisted. On Day+32, he developed severe hypotension, requiring multiple inotropes, and acute hypoxemia requiring intubation and mechanical ventilation. Echocardiogram showed mildly increased right ventricle systolic pressure necessitating treatment with nitric oxide.

Given worsening clinical status, the patient underwent comprehensive evaluation for superimposed infections. A repeated COVID-19 test remained positive. Blood cultures grew *Staphylococcus epidermidis* , and antibiotic coverage was broadened. A *Candida parapsilosis* infection was treated with double anti-fungal coverage, and BK and Cytomegalovirus viremias were treated with cidofovir and letermovir, respectively.

Primary graft failure was diagnosed by: 1) a bone marrow biopsy showing less than 5% cellularity, 2) absence of donor specific antibodies, 3) compatible forward and backward flow cytometric crossmatches, and 4) absence of donor marrow CD33+ cells. On day +39 post-transplant, conditioning with fludarabine for three days was started in preparation for a second haploidentical related CD34 selected peripheral HSC infusion. Due to worsening hypotension and multisystem organ failure, salvage therapy with a second unit of CCP and a third dose of tocilizumab was given on Day +41. However, despite all efforts he died on Day +42 post-transplant.

Discussion

Available pediatric clinical data on COVID-19 show that children usually have a more indolent disease course, but evidence regarding immunocompromised patients is limited.

The incubation period, duration of viral shedding, onset and duration of symptoms, viral detection, and lab findings may differ in immunocompromised patients with COVID-19 compared to their immunocompetent counterparts. Additionally, immunocompromised patients are at increased risk for secondary infections and for progression to severe disease; responses to supportive care measures and future antiviral therapies may also differ.[11]

Studies have shown that T-cell reduction is common in severe cases of COVID-19 infection, demonstrating that the virus may act mainly on T-lymphocytes. In another case report, two adult post-transplant patients were depicted: one was an allogeneic HSCT recipient and the other, a kidney transplant recipient.[12] Both were under immunosuppressive therapy when infected with the virus and had adequate grafts function, but

both eventually died after developing multi-organ failure. Hence, a severely immunocompromised patient can experience a more severe disease course with a poorer outcome.

In an effort to prevent a rapid clinical deterioration and ensure graft preservation, our patient was treated aggressively. As shown in Table 1, a decrease in inflammatory markers was noted at first, which we associated to achieving viral load control with remdesivir. However, we believe that the COVID-19 significantly affected stem cell engraftment, leading to multisystemic infections that reversed the improving trend in inflammatory markers, which also corresponded with the onset of hypotension. The combination of a lack of anti-viral drug and hypotension from bacterial and fungal infections led to his rapid deterioration.

As depicted in our case, COVID-19 infection in severely immunocompromised patients can be life-threatening, and the effects of SARS-CoV-2 in this patient population are highlighted. First, the treatment with remdesivir and tocilizumab showed temporary amelioration of CRS. Second, either direct viral toxicity or overwhelming CRS significantly affected our patient's engraftment. Third, more widely available treatments are needed to treat the most vulnerable patients; the impact of a prolonged anti-viral course is still unknown. Ultimately, despite the best available treatments for COVID-19, the patient developed multiple infections likely secondary to primary graft failure that progressed to multi-system organ failure and death.

Conflict of Interest Statement

There are no conflicts of interest to disclose.

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FIGURE 1 Chest Computer Tomography showing “groundglass” opacities consistent with COVID-19 infection.