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Allogeneic Hematopoietic Stem Cell Transplant for Acute Lymphoblastic Leukemia in a Pediatric Patient After COVID-19 Infection Complicated by MIS-C

Kayleigh M. Schwartz, MS, RN, CPNP-PC, Chelsea Honstain, MSN, RN, FNP, Jessica L. Spruit, DNP, RN, CPNP-AC, & Megan Harris, DNP, RN, CPNP-PC

The COVID-19 pandemic has impacted the care of countless individuals, including pediatric oncology patients. The initial lack of knowledge about the disease course and implications of infection led to delays in treatment to minimize additional harm. In pediatric oncology, unnecessary delays in chemotherapy or hematopoietic stem cell transplantation may increase the risk of disease relapse. This case report describes one high-risk pediatric oncology patient's clinical course through hematopoietic stem cell transplantation immediately following COVID-19 infection complicated by multisystem inflammatory syndrome in children. The disease course, monitoring, long-term outcome, and recommendations for future research are reviewed. J Pediatr Health Care. (2022) *36*, 280–285

KEY WORDS

Hematopoietic stem cell transplant, COVID-19, MIS-C, leukemia, pediatrics

INTRODUCTION

The COVID-19 pandemic has greatly impacted the care of pediatric oncology patients worldwide. Although pediatric patients generally have a milder disease course, concerns remain regarding the increased risk of severe complications in immunocompromised populations. There is a paucity of

Kayleigh M. Schwartz, Nurse Practitioner, Blood and Marrow Transplant Program, Division of Pediatric Hematology/Oncology, Department of Pediatrics, University of Michigan, Ann Arbor, MI.

Chelsea Honstain, Nurse Practitioner, Blood and Marrow Transplant Program, Division of Pediatric Hematology/Oncology, Department of Pediatrics, University of Michigan, Ann Arbor, MI.

Jessica L. Spruit, Nurse Practitioner, Blood and Marrow Transplant Program, Division of Pediatric Hematology/Oncology, Department of Pediatrics, University of Michigan, Ann Arbor, MI.

Megan Harris, Nurse Practitioner, Blood and Marrow Transplant Program, Division of Pediatric Hematology/Oncology, Department of Pediatrics, University of Michigan, Ann Arbor, MI.

Conflicts of interest: None to report.

Consent was provided by the patient's parents to publish information regarding his medical condition and treatment.

Correspondence: Kayleigh M. Schwartz, MS, RN, CPNP-PC, Blood and Marrow Transplant Program, Division of Pediatric Hematology/Oncology, Department of Pediatrics, University of Michigan, 1500 E. Medical Center Dr., Ann Arbor, MI 48109; e-mail: kayhedr@med.umich.edu.

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data on children with cancer presenting with COVID-19 infection and optimal management of their oncological disease and concurrent viral infection.

Although pediatric oncology patients have had similar comorbidities to adult oncology patients, they have experienced less symptomology and lower mortality rates than their adult counterparts (Belsky et al., 2021). Avoidance of intensive chemotherapy or a moderate reduction of chemotherapy during the acute phase of illness with severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection is recommended (El Dannan, Al Hassani, & Ramsi, 2020; Sahu, Siddiqui, & Cerny, 2020); however, this must be balanced with their cancer treatment as delays may lead to progression of their underlying malignancy and increase mortality risk. This case report examines the allogeneic hematopoietic stem cell transplant (HSCT) course of a pediatric patient with B-cell acute lymphoblastic leukemia (B-ALL) who was diagnosed and treated for COVID-19 and multisystem inflammatory syndrome in children (MIS-C) 12 weeks before an unrelated donor HSCT.

CASE PRESENTATION

A 3-year-old male was diagnosed in April 2019 with B-ALL CD19^{+}, CD45^{+}, with KMT2A/MLLT1 rearrangement, (t [11:(19) (q23:p13)]) and received chemotherapy according to a standard risk Children's Oncology Group protocol. He achieved initial remission only after an isolated marrow relapse in October 2020 during maintenance therapy. On day 19 of reinduction therapy (day one of illness), the patient developed febrile neutropenia. His initial blood cultures returned positive for *Rothia mucilaginosa,* and cefepime and vancomycin were prescribed. Further chemotherapy was deferred because of febrile neutropenia, bacteremia, and concern for sepsis.

On day three of illness, the patient remained persistently febrile and tachycardic despite broad-spectrum antimicrobials. He required fluid resuscitation and increased transfusion support to maintain hemodynamic stability. In addition, a high-flow nasal cannula was prescribed. When his respiratory symptoms did not improve the following diuresis, a nasopharyngeal COVID-19 polymerase chain reaction (PCR) was obtained, resulting in a positive result. Following consultation with the Pediatric Infectious Disease team, MIS-C serological studies were obtained, including complete blood counts, procalcitonin, C-reactive protein (CRP), serum ferritin, complete metabolic panel, D-dimer, and brain natriuretic peptide (BNP; Table 1). Although his serum D-dimers were elevated and concerning for a hypercoagulable state, deep vein thrombosis prophylaxis was held because of concurrent thrombocytopenia. A five-day course of remdesivir was prescribed. Convalescent plasma was considered; however, his COVID-19 IgG testing resulted positive, rendering him ineligible.

Given the risk of cardiac complications in hyperinflammatory states, an echocardiogram (ECHO) was obtained on day five of illness and revealed low-normal function and dilated right coronary artery without aneurysm in addition

TABLE 1. Multisystem inflammatory syndrome in children (MIS-C) laboratory trends

Variable	CRP, mg/100 ml	Procal, ng/ml	ESR, mm	D-dimer, mg/L FEU	BNP, pg/ml	Ferritin, ng/ml
Level at presentation	22.30	5.50	30	0.96	580	768.70
Peak level	31.40	40.43	110	4.90	2,822	2,878
	(day 3 of illness)	(day 6 of illness)	(day 22 of illness)	(day 7 of illness)	(day 6 of illness)	(day 10 of illness)
Following COVID-19 MIS-C treatment (29 days)	< 0.20	0.18	36	0.33	20	1,756.50
Before HSCT	< 0.20	0.14	23	0.60	11	1,735.50

Note. *BNP, brain natriuretic peptide; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FEU, fibrinogen equivalent units; HSCT, hematopoietic stem cell transplant; Procal, procalcitonin.*

TABLE 2. Serum cytokine levels on day one and 22 following diagnosis of COVID-19 infection and multisystem inflammatory syndrome in children (MIS-C)

Inflammatory biomarker	Reference (pg/ml)	Day 1	Day 22
TNF-α	≤ 7.0	10.6	< 1.7
IFN-γ	≤ 4.2	4.5	< 4.2
IL-1	≤ 6.7	23.3	< 6.5
IL-2R	175–858	2,658.1	746
IL-6	≤ 2.0	237.9	6.8
IL-8	≤ 3.0	136.3	3.0
IL-13	≤ 2.3	202	< 1.7

Note. *Day one of illness, time of MIS-C diagnosis; day 22 of illness, status post-treatment with Anakinra; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor*.

to a small pericardial effusion. The patient continued to be febrile with significantly elevated inflammatory markers. A panel of cytokines and inflammatory proteins were measured at this time, with serum levels of interleukin (IL)-2R, IL-6, IL-8, and IL-13 markedly elevated (Table 2). In addition, serum CRP, ferritin, BNP, and D-dimer levels continued to increase (Table 1). At this time, the patient met the Centers for Disease Control and Prevention criteria for MIS-C and anakinra, an IL-1 receptor antagonist, and two doses of intravenous immunoglobulin were administered. Systemic corticosteroids were not initially used because of prolonged neutropenia and concurrent bacteremia; however, dexamethasone was prescribed for a 10-day course on the seventh day of illness. The patient's clinical status and serological studies (complete blood counts, CRP, procalcitonin, erythrocyte sedimentation rate, D-dimer, BNP) showed initial improvements with these measures. On the basis of the microbiologic sensitivity assays for the *Rothia mucilaginosa,* his antimicrobial coverage was modified, with the patient completing a seven-day treatment course of clindamycin with empirical antibiotics continuing because of his ongoing neutropenia.

On day 10 of illness, the patient was in septic shock with persistent fever, fluid refractory hypotension, and a precipitous hemoglobin drop. He required multiple fluid boluses and platelet and red cell transfusions. Given his prolonged neutropenia, his empirical antibiotics were again broadened per institutional standards. Repeat blood and urine cultures demonstrated no additional infections, and antibiotics were then de-escalated with improved clinical status on day 14 of illness. Once stabilized, the patient resumed vincristine for leukemic disease control.

Although inflammatory markers initially improved with anakinra and a 10-day systemic steroid course, the patient continued to experience recurrent daily fevers and ongoing tachycardia. Repeat COVID-19 testing on days 16 and 17 of illness were negative. A repeat ECHO showed a decreased ejection fraction from the previous study with the low-normal systolic function of the left ventricle, left ventricular global strain decreased, and pericardial effusion. An interleukin panel was repeated on day 22 of illness and showed normal to improved values of IL-2R, IL-6, IL-8, and IL-13 (Table 2). Therefore, anakinra was discontinued; however, because of the patient's clinical picture and worsening fever curve, methylprednisolone was resumed on day 23 of illness. An infectious workup was completed, including viral and fungal studies and computed tomography of the sinuses, chest, abdomen, and pelvis with no obvious infection source.

Given concern for thrombosis in MIS-C, aspirin was also initiated on day 25 of illness. The patient's clinical status and serological studies, specifically his serum CRP, ferritin, BNP, and D-dimer, began to improve after the initiation of methylprednisolone. Following resolution of symptoms, he was transitioned to oral steroids on day 26 of illness with a slow corticosteroid taper planned. He was tapered off systemic corticosteroids after seven weeks of treatment.

A repeat marrow aspirate and biopsy revealed a remission status and minimal residual disease negative, and he proceeded with consolidation chemotherapy per protocol on day 34 of illness. After completion of consolidation therapy, he consented to HSCT because of his history of early leukemic relapse. A pretransplant workup ECHO revealed improved cardiac function with resolved pericardial effusion. Baseline computed tomography scans were repeated post-COVID-19/MIS-C and before HSCT and were negative for infectious processes.

The patient was admitted for a matched unrelated allogeneic HSCT 12 weeks post-COVID-19/MIS-C treatment. By the time of admission, his serologic markers for inflammation had normalized (Table 1). He completed a myeloablative preparative regimen of cyclophosphamide and total body irradiation (1,200 cGy) followed by a 10/10 human leukocyte antigen matched unrelated allogeneic stem cell transplant with a cell dose of 3.8×10^6 $CD34^+$ cell/kg and 6×10^8 total number of nucleated cells/kg. He received tacrolimus, methotrexate, and an investigational agent, vorinostat (NCT03842696), for graft-versus-host disease (GVHD) prophylaxis. He received infection prophylaxis and monitoring per institutional guidelines. The patient experienced oral candida during his conditioning regimen and was treated with oral nystatin.

He developed an isolated fever on day eight post-transplant following a platelet transfusion. Blood and urine cultures were negative; however, his antibiotics were broadened to empirical cefepime per institutional guidelines through

neutrophil recovery. He engrafted neutrophils on day 12 post stem cell infusion. His post-transplant course was complicated by *Clostridium difficile* infection that was first identified on day 19 post-transplant and he completed a 10-day treatment course of oral vancomycin. He required total parenteral nutrition for 14 days because of large volume diarrhea, decreased oral intake and intolerance of enteral feeds. Serial electrocardiograms were monitored throughout hospitalization because of persistent tachycardia and were unremarkable (sinus tachycardia). He was discharged home on day 25 post-HSCT.

His day 30 post-HSCT evaluation revealed an erythematous macular rash on the surface of his face in addition to scattered erythematous papules on his truncal surface (< 25% of body surface area), consistent with stage 1 skin GVHD. Topical triamcinolone and hydrocortisone were initiated, and his vorinostat dose was adjusted per investigational protocol. A bone marrow biopsy revealed a negative minimal residual disease status, fluorescence in situ hybridization negative for mixed-lineage leukemia rearrangement, CD3 chimerism 98% donor, and CD33 chimerism 100% donor. An ECHO was also completed because of his history of COVID-19/MIS-C, which revealed normal bilateral ventricular function without hypertrophy and stable left ventricular ejection fraction at 58%.

DISCUSSION

For the general population who test positive for COVID-19, few individuals can transmit the virus after 10 days from symptom onset (Centers for Disease Control and Prevention [CDC], 2020). In severely immunocompromised patients, viral shedding has been noted to last much longer, with PCR results remaining positive for weeks to months post initial infection (Sahu et al., 2020). This prompts concern regarding decisions to proceed with oncology treatment plans and the potential for recurrence of COVID-19 symptoms. Immunocompromised children have had favorable outcomes despite COVID-19 infections and when receiving necessary treatment for their malignancies without severe adverse effects (El Dannan et al., 2020).

HSCT is an example of treatment that needs to be carefully considered for oncology patients with COVID-19 infection. Seven adult patients with acute leukemia who received allogeneic HSCT post-COVID-19 infections did not experience a more complicated post-transplant course (Christopeit et al., 2021). In addition, no reactivation of COVID-19 was observed here (Christopeit et al., 2021). Current recommendations from the American Society for Transplantation and Cellular Therapy for patients undergoing HSCT or cellular therapy who are acutely infected with COVID-19 are to defer transplant or cell infusion for a minimum of 14–21 days with at least two consecutive negative PCR tests spaced 24 hr apart with the absence of symptoms (Waghmare et al., 2020). For patients with high-risk underlying diseases, careful consideration on a case-by-case basis regarding the decision to proceed with transplant is recommended (Waghmare et al., 2020).

Additional considerations in the progression of oncological management also include the hyperinflammatory response associated with COVID-19. As the pandemic progressed, it became evident that children presented with different symptoms than adults. Numerous pediatric cases presented hyperinflammatory shock and multiorgan system involvement similar to Kawasaki's disease (Ahmed et al., 2020). These children exhibited high inflammatory markers (IL-6, ferritin, erythrocyte sedimentation rate, CRP), persistent fever, rash, gastrointestinal, cardiovascular, and respiratory symptoms (Feldstein et al., 2020). In most of these cases, children were shown to be positive for SARS-CoV2 either via real-time polymerase chain reaction or serological testing or were known to have recent direct exposure to an infected individual (Feldstein et al., 2020). As more cases evolved globally, the Centers for Disease Control and Prevention, the World Health Organization, and the Royal College of Paediatrics and Child Health labeled this illness MIS-C (Table 3; CDC, 2020; World Health Organization [WHO], 2020).

The current hypotheses of the emergence of MIS-C are attributed to a delayed immunologic response to COVID-19 infection, molecular mimicry, and viral superantigens that activate an immunologic host response to virus-infected cells mediated by antibodies, T-cells, or macrophages (Belay et al., 2021; Pandrowala et al., 2021). A cross-sectional study identified 1,816 pediatric patients in the United States as having met the diagnostic criteria for MIS-C (Belay et al., 2021). Children hospitalized with COVID-19 also exhibited clinical manifestations that overlapped with that of MIS-C (Belay et al., 2021). Although available literature and data expand on general pediatric patients who have experienced this syndrome, there are limited data describing the clinical course of pediatric oncology patients who have MIS-C. Two case studies have described pediatric patients with leukemia who presented with SARS-CoV2 related MIS-C; in one case, the patient was treated with methylprednisolone, and in the other case, no specific MIS-C treatment was prescribed. Both patients recovered and proceeded with their oncological treatment plan (Al-Haddad et al., 2020; Pandrowala et al., 2021).

Because of limited published literature on pediatric oncology patients with COVID-19 and MIS-C, universal recommendations for the management of such patients continues to evolve. We follow the American Society of Transplant and Cellular Therapies and published guidelines for managing COVID-19 exposure (or infections) in our HSCT recipients, including the guidelines for the diagnosis and management of MIS-C in the general pediatric population (Waghmare et al., 2020). HSCT recipients who survive COVID-19 infections and MIS-C may require surveillance and follow-up unique to their infection and inflammatory complications, in addition to standard post-HSCT organ function monitoring. It is essential that the health care providers directing post-transplant care have awareness of current recommendations regarding MIS-C, as they are often the health care provider that the patient has the most

TABLE 3. Summary of Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) multisystem inflammatory syndrome in children (MIS-C) criteria

WHO[1] All criteria must be met:

1. Aged 0–19 years with fever for ≥ 3 days
2. clinical signs of multisystem involvement (at least 2):
   1. Rash, bilateral nonpurulent conjunctivitis or mucocutaneous inflammation signs (oral, hands or feet)
   2. Hypotension or shock
   3. Cardiac dysfunction, pericarditis, valvulitis or coronary abnormalities
   4. Evidence of coagulopathy
   5. Acute gastrointestinal symptoms
3. Elevated markers of inflammation.
4. No other obvious microbial cause of inflammation.
5. Evidence of SARS-CoV2 infection (RT-PCR, serology or antigen test; or exposure within 4 weeks before the onset of symptoms)

CDC[2] All criteria must be met:

1. Aged < 21 years with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization with multisystem (> 2) organ involvement
2. No alternative diagnoses
3. Positive for current or recent SARS-CoV2 infection by RT-PCR, serology or antigen test; or exposure within 4 weeks before onset of symptoms

Note. *This table outlines the CDC and WHO case definitions of MIS-C. Patients who meet these criteria and fulfill full or partial criteria for Kawasaki's disease should be considered to have MIS-C and should be reported. In addition, MIS-C should be considered in any pediatric death with evidence of SARS-CoV-2 infection (CDC, 2020). Laboratory evidence of inflammation: C-reactive protein, erythrocyte sedimentation rate, lactate dehydrogenase, interleukin-6, brain natriuretic peptide, brain natriuretic peptide, fibrinogen, procalcitonin, d-dimer, elevated neutrophils, reduced lymphocytes, and low albumin (CDC, 2020). Laboratory evidence of coagulopathy: prothrombin time, partial prothrombin time, and elevated d-dimer (WHO, 2020).*

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; RT-PCR, real-time polymerase chain reaction.

[a]World Health Organization (2020). Multisystem inflammatory syndrome in children and adolescents temporally related to COVID-19. Scientific brief. https://www.who.int/news-room/commentaries/detail/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19. [b]Centers for Disease Control and Prevention. (2021). Information for health care providers about multisystem inflammatory syndrome in children (MIS-C). https://www.cdc.gov/mis/mis-c/hcp/index.html.

frequent and ongoing contact with the immediate post-transplant period. Current guidance is available from the American College of Rheumatology and includes recommendations to perform serial and ongoing monitoring on the basis of disease manifestations at the time of illness (Henderson et al., 2021).

We recognize the limitations of our single case-study patient. The experience of one patient at our institution may not be representative of broader transplant outcomes. However, our case summarizes a unique illness trajectory and adds to the paucity of literature related to the safety and feasibility of HSCT following COVID-19 infection complicated by MIS-C. There are several reports of children with hematologic and oncological diagnoses becoming infected with COVID-19 (Gampel et al., 2020). In addition, there are case reports and summaries of patient experiences when infected with COVID-19 following HSCT (Vicent et al., 2020). There is very limited published experience for HSCT patients following COVID-19 infection and no case reports of HSCT following COVID-19 infection complicated by MIS-C (Christopeit et al., 2021; Cuzzubbo et al., 2021; Stanley, Hanmod, Simpson, & Katsanis, 2021). The effects of COVID-19 infection and MIS-C before HSCT and their potential for inducing post-transplant complications, specifically transplant-associated vasculopathy complications (sinusoidal obstruction syndrome, transplant-associated thrombotic microangiopathy, high-grade GVHD) and effects of the SARS-CoV2 virus on graft function require further investigation. The development of guidelines for long-term post-transplant care for HSCT recipients who have survived COVID-19 and MIS-C is needed.

Conclusions

Our case report highlights the successful transplant of a pediatric patient with high-risk B-ALL who underwent an unrelated donor HSCT within 12 weeks following treatment for COVID-19 and MIS-C. The patient did not experience post-transplant complications, including sinusoidal obstruction syndrome, transplant-associated thrombotic microangiopathy, or high-grade GVHD despite theoretical increased risk because of his prior hyperinflammatory state and vasculopathy associated with his prior hyperinflammatory state and vasculopathy recent COVD-19 infection and MIS-C. His day 30 post-HSCT evaluation revealed continued remission from leukemia with improving cardiac function, overall stable organ function, and no long-term effects from COVID-19 infection or MIS-C to date. The patient is only 80 days post-HSCT with long-term follow-up pending.

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