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LETTER TO THE EDITOR

Posthematopoietic stem cell transplant COVID-19 infection in a pediatric patient with IPEX syndrome

To the Editor:

December 2019 marked the emergence of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[8,9] Several treatment approaches are under study. The antiviral remdesivir[10] has been shown to improve overall mortality in patients treated for COVID-19,[1] and was approved by the United States Food and Drug Administration (FDA) for hospitalized patients with severe disease.[2] Tocilizumab, a humanized antiinterleukin-6 receptor[11] antibody, can hasten COVID-19-related cytokine release syndrome recovery by 75%.[3] Implementation of COVID-19 convalescent plasma (CCP) in the treatment of COVID-19 infection was also suggested by the FDA.[4]

An 8-year-old African-American male with immune-dysregulation polyendocrinopathy X-linked (IPEX) syndrome underwent haploidentical, related bone marrow hematopoietic stem cell transplant (HSCT), and contracted SARS-CoV-2 during the periengraftment period, subsequently developing primary graft failure. The conditioning regimen included busulfan, fludarabine, rabbit antithymoglobulin, and posttransplant cyclophosphamide; graft versus host disease (GVHD) prophylaxis consisted of mycophenolate mofetil and cyclosporine.

Lack of engraftment and fever were noted on Day + 21 posttransplant. A sedated bone marrow aspiration was planned; prior to sedation he tested positive for COVID-19 via nucleic acid amplification test. Development of respiratory distress prompted a chest CT that showed "bilateral ground-glass opacities" (Figure 1); noninvasive ventilation was initiated. A 10-day-course treatment with remdesivir began on Day + 26.

We trended inflammatory parameters daily (Table 1), and based our treatment decision on a calculated H-score[5] of 209, which correlated with a 92.8% risk probability of cytokine release syndrome. Two doses of tocilizumab and one unit of CCP[12] were given. On Day + 32, severe hypotension, acute hypoxemia, and mildly increased right ventricle systolic pressure ensued, requiring mechanical ventilation and nitric oxide. A comprehensive evaluation for superimposed infections was remarkable for a repeated positive SARS-CoV-2 test, *Staphylococcus epidermidis* and *Candida parapsilosis* infections, and BK and cytomegalovirus viremias.

Bone marrow aplasia, lack of donor marrow CD33+ cells, absence of donor-specific antibodies, and compatible forward and backward flow cytometric crossmatches confirmed primary graft failure and immune rejection, commonly seen in patients with IPEX syndrome. In preparation for a second haploidentical related CD34+ selected peripheral hematopoietic stem cell infusion, conditioning with fludarabine for 3 days began on Day + 39 posttransplant. 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 posttransplant.

Compared to their immunocompetent counterparts, immunocompromised patients with COVID-19 are at increased risk for secondary infections and progression to severe disease, as well as a different response to supportive care measures.[6] Studies have shown that SARS-CoV-2 acts mainly on T-lymphocytes; hence, a severely immunocompromised patient experiences a poorer outcome. A case report depicted two adult posttransplant patients with adequate graft function, on immunosuppressive therapy, that eventually died after developing multiorgan failure.[7]

Our patient was treated aggressively, and we attributed the first decreasing trend in inflammatory markers (Table 1) to achieving disease control. However, the combination of graft failure, COVID-19 infection with multiorgan failure, and opportunistic infections contributed to his death. We hope that new treatments continue to stem from ongoing research, to achieve a different outcome in our patient population.

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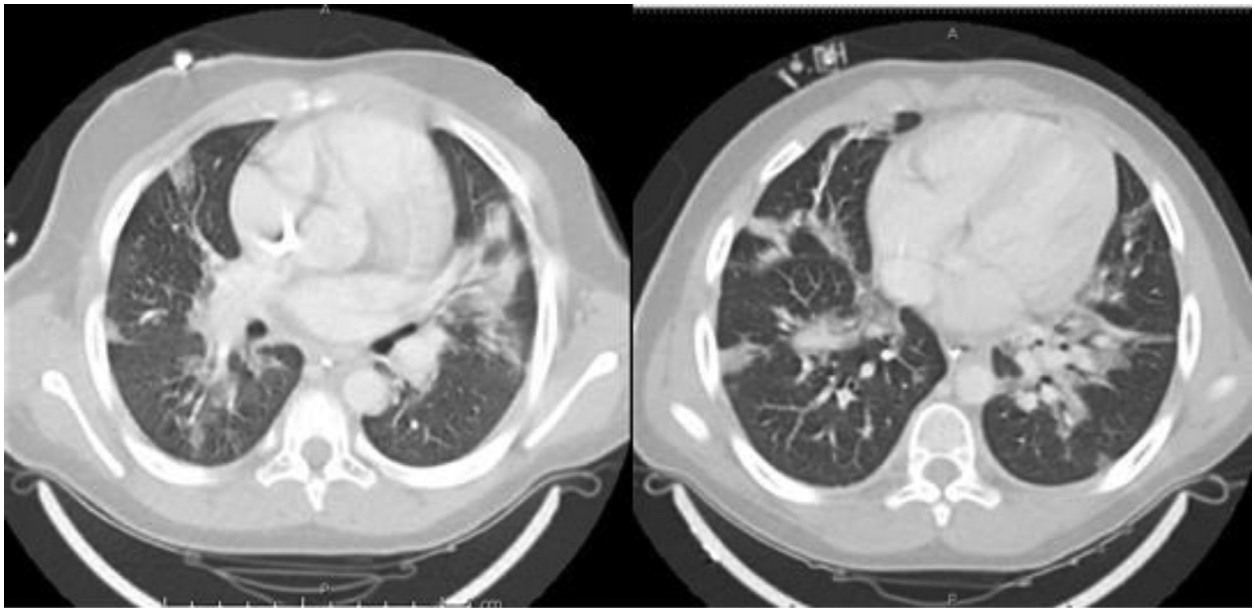

FIGURE 1 Chest computer tomography showing "ground-glass" opacities consistent with COVID-19 infection

TABLE 1 Inflammatory markers trend after starting treatment for COVID-19 infection

		Inflammatory markers				
COVID treatment day	Days posttransplant	Ferritin (ng/mL)	Procalcitonin (ng/mL)	LDH (U/L)	CRP (mg/dL)	D-dimer (ug/mL FEU)
Day −2	24	7790	0.5	432	9.87	13.4
Day −1	25	14 167	0.68	626	10.8	**18.31**
Start of treatment[a,b]	**26**	**14 272**	1.04	780	11.8	17.11
Day 2[c]	27	13 619	**2.39**	1019	**16.2**	16.5
Day 3[d]	28	13 871	1.65	**1092**	8.9	13.6
Day 4	29	10 532	1.18	1021	4.2	11.62
Day 5	30	8797	0.66	962	2.3	9.67
Day 6	31	8496	0.51	1018	1.7	10.62
Day 7	32	6594	0.33	827	1.1	8.9
Day 8	33	6533	0.18	857	0.7	8.45
Day 9	34	5153	0.45	719	1.1	12.99
Day 10[e]	35	4971	0.7	629	4.5	10.55
Day 11	36	6066	0.57	645	4	5.96
Day 12	37	5145	0.64	801	5.2	8.13
Day 13	38	4648	0.69	945	5	8.39
Day 14	39	6588	0.85	1208	4.2	7.92
Day 15	40	8727	0.81	1140	3	7.09
Day 16[f,g]	41	10 294	1.5	1136	2.3	8.01
Day 17	**42**	**28 884**	**2.99**	1093	2.2	9.33

Note. Highest values are highlighted for each inflammatory marker.

[a] First dose of remdesivir.

[b] First dose of tocilizumab.

[c] Second dose of tocilizumab.

[d] First convalescent plasma transfusion.

[e] Treatment with remdesivir completed.

[f] Third dose of tocilizumab.

[g] Second convalescent plasma transfusion.

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