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CASE REPORT

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Varying presentations of COVID-19 in young heart transplant recipients: A case series

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Abstract

Background: Immunosuppression is considered a risk factor for more severe clinical presentation of COVID-19. Limited data regarding clinical outcome exist in adults, whereas very little is known about the spectrum of the disease in pediatric heart transplant recipients.

Methods: We retrospectively reviewed the charts of young heart transplant patients from our tertiary care center during the coronavirus pandemic in New York City and identified patients infected with SARS-CoV-2.

Results: We present four cases with COVID-19 disease and elaborate on their presentation and clinical course.

Conclusions: Although far from conclusive and limited by the small sample size and selection bias, these cases demonstrate mild and self-limited disease despite immunosuppressive therapy and various comorbidities that are expected to increase the severity of the clinical picture based on extrapolation from the adult experience with this novel disease.

KEYWORDS

COVID-19, pediatrics, heart transplantation, immunosuppression

1 | INTRODUCTION

As the COVID-19 pandemic continues to evolve, the medical community is faced with unexpected presentations in different patient populations. Data on heart transplant recipients are quite limited in adults[1-8] and lacking in children. One would expect that these patients are particularly vulnerable and at risk for more severe disease given their immunocompromised status and the high prevalence of comorbidities such as diabetes, hypertension, and chronic kidney disease.[9] However, it is currently unclear whether chronic immunosuppression is a risk factor for more severe disease and prolonged viral shedding, or it actually has a protective role by attenuating a dysregulated immune response and dampening the cytokine release syndrome that is associated with severe disease.[4] Consequently, the optimal management of immunosuppression upon diagnosis of COVID-19 disease remains unknown.

We herein discuss four cases of young heart transplant recipients infected with COVID-19 and review the clinical presentation, treatment strategies, and short-term outcome.

2 | CASE 1

A 15-year-old girl with history of familial dilated cardiomyopathy status post–third heart transplant and first kidney transplant 5 months ago, presented with fever, cough, abdominal pain, decreased oral intake, and fatigue. Her outpatient immunosuppression included cyclosporine, mycophenolate sodium, and low-dose

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

prednisone. She had recently completed total lymphoid irradiation as well.

Upon transfer from an outside hospital, she was afebrile with a heart rate of 109 bpm, blood pressure of 108/64 mm Hg, and oxygen saturation of 90%-93% on 2 L nasal cannula O2. Her chest radiograph was unremarkable. The ECG demonstrated sinus tachycardia, right atrial enlargement, and non-specific T-wave abnormalities, unchanged from prior ECGs. Her echocardiogram had normal biventricular function, mild-to-moderate tricuspid regurgitation, and hypokinetic septal wall motion, also unchanged from prior. Laboratory analysis showed WBC 1460/μL with an absolute neutrophil count of 800 cells/μL. Other notable laboratories included elevations in ferritin 345.6 ng/mL, CRP 55.10 mg/L, D-dimer 1.49 μg/mL, pro-BNP of 440.8 pg/mL, but a negative high-sensitivity troponin—T of 21 ng/L. BUN and creatinine were stable at 16 mg/dL and 0.82 ng/dL, respectively. She tested positive for COVID-19.

Following admission, her mycophenolate sodium and valganciclovir were held due to an ANC <500. She was weaned off of her supplemental oxygen over three days. At discharge, her oxygen saturation was 96% on room air with normal vital signs for age. She received no COVID-19-specific therapies. She received two doses of filgrastim and the mycophenolate sodium has continued to be held for six weeks at the time of this writing. She was seen via a remote telehealth visit nine days post-discharge and was noted to be stable with no new symptoms.

Our patient was less than six months post–multiorgan transplant and given her retransplantation status and recent enhanced immunosuppression, she presented challenges in achieving therapeutic immunosuppression while managing her neutropenia. The cause of her neutropenia was probably multifactorial but mostly due to her immunosuppression regimen. The COVID-19 infection was mild and self-limited; however, it is conceivable that it could have also contributed to her marrow suppression.

3 | CASE 2

A 25-year-old woman still under the care of our pediatric center with history of dilated cardiomyopathy initially transplanted as an infant, now status post–second heart and first kidney transplant 3 years prior. She presented with a two-day history of fever to 101 Fahrenheit, chills, sore throat, cough, nausea, extreme lethargy, and decreased oral intake. She did not have shortness of breath or dyspnea. Her father was hospitalized with COVID-19 pneumonia, and she tested positive for COVID-19, as well. Her immunosuppression included cyclosporine, azathioprine, and prednisone. Her history was also significant for long-term Raynaud's phenomenon since early adolescence. Due to history of renal rejection and early significant coronary vasculopathy, she underwent work-up in late 2019 that revealed connective tissue disease with massive elevations of soluble IL-2 receptor and IL-2. Therefore, at the time of COVID-19 infection, she was also being treated with monthly belatacept (to spare high CNI use for her kidney), basiliximab (for her connective tissue disease), and bolus methylprednisolone infusions as well as oral hydroxychloroquine every other day.

Following her initial presentation, she continued to have mild symptoms for an additional four days. She did not require admission to the hospital and was followed closely via telehealth. Given that this patient was profoundly immunosuppressed, with an underlying connective tissue disease, and older than the rest of our patients, one might expect worse pulmonary complications with COVID-19 and higher risk of bacterial or fungal super-infection. She also did not develop worsening renal function or thromboses as could happen with a fragile kidney and Raynaud's disease. The question of determining whether this patient had a mild course because she was already on a regimen of hydroxychloroquine cannot be answered definitively. Despite various recommendations regarding the efficacy of hydroxychloroquine, its benefits to patients affected with COVID-19 at this time remain unproven, at best.

4 | CASE 3

A 13-month-old, ex full-term boy with history of hypoplastic left heart syndrome with failed Norwood physiology status post–positive cross-match (CDC T- and B-cell positive) heart transplant 6 months prior, complicated by early cellular and antibody-mediated rejection. He received total blood exchange and antithymocyte globulin immediately postoperatively. One month later, he received a further five rounds of blood volume exchange and rituximab and IVIG infusions due to severe combined antibody-mediated and cellular rejection. He had remained well for five months when his mother was diagnosed with COVID-19 due to fever, cough, and wheezing and was hospitalized for eight days. The patient remained well for the entire month after the mother's hospitalization and presented for a scheduled heart biopsy. The mother reported that he developed mild non-productive cough and sneezing that morning. He underwent COVID-19 testing prior to the procedure per institutional protocol, tested positive, and the procedure was canceled. His immunosuppression at the time included tacrolimus, mycophenolate mofetil, and low-dose prednisone.

Given his minor symptoms, normal examination, echocardiogram and ECG, as well as a normal WBC count, CRP, electrolytes, and liver function tests, the patient was sent home with no change in his medications. His IL-6 came back normal, and his CD3 count was low, as was his Immuknow at 43, indicative of a very immunosuppressed state. Subsequently, his EBV PCR came back as elevated for the first time. He has been followed closely with telehealth visits since then and he is currently asymptomatic. Despite his intense immunosuppression regimen, this patient, who is the youngest in our series, had very mild disease. The impact of immunosuppression as well as the role of age in the lack of severity of disease in this mostly asymptomatic infant is important considerations highlighted by this case.

5 | CASE 4

A 29-month-old girl with history of familial dilated cardiomyopathy status post–heart transplant 2 years prior, presented with pallor, fatigue, decreased oral intake, and papular rash over elbows and knees for seven days. Her outpatient immunosuppression included tacrolimus and azathioprine. Of note, multiple household members had COVID-19 four weeks prior to her admission. She herself had two days of fever and cough at that time, but was not seen by a healthcare provider because she appeared well, while other family members were hospitalized with serious infection. Her admission laboratories were notable for Hgb of 6.2 g/dL and elevated transaminases (peak ALT 1807 U/L and peak AST 1070 U/L). The inflammatory markers were unremarkable, and the nasopharyngeal swab PCR was negative for SARS-CoV-2. She was transfused and underwent a transcutaneous liver biopsy on hospital day 5 that was consistent with viral hepatitis (negative for COVID-19). Her rash was diagnosed as an acral papular eruption (Gianotti-Crosti), also consistent with viral etiology. Repeat nasal PCR for COVID-19 was still negative and parvovirus PCR was also negative but SARS-CoV-2 serology by ELISA technique (test developed in our lab) came back positive, confirming she had a prior infection.

This case highlights a mildly symptomatic COVID-19 infection followed by a constellation of symptoms (anemia, hepatocellular injury, and rash) that point to a post-viral etiology. Parvovirus could explain her clinical presentation; however, her positive COVID-19 serologies and the fact that the rest of the viral work-up was negative (including Parvovirus, EBV, CMV, and hepatitis viruses) make it plausible that this clinical presentation is secondary to COVID-19 even though the liver biopsy was negative for COVID-19 staining. There are a multitude of rashes reported post-COVID-19, and this literature is still expanding. It is also interesting that our patient's presentation has a similar temporal relationship to the primary COVID-19 infection as the pediatric cases now presenting with multisystem inflammatory syndrome, although her course was much milder.

6 | DISCUSSION

The COVID-19 pandemic has presented the medical community with unique challenges. Knowledge regarding outcomes of at-risk patient groups such as transplant recipients is still evolving. Based on the majority of the reports on adult solid organ transplant recipients, current literature supports favorable outcomes in this population. However, numbers reported are limited and conclusions are difficult to draw based on such limited and frequently conflicting data. Cases of more severe disease including fatalities have also been reported[7,10] and a recent study on adult solid organ transplant recipients, including nine post–heart transplant (10% of the study cohort), documented more severe disease in this population, although the authors acknowledged that testing limitations led to undercounting of mild/asymptomatic cases.

The general approach followed in the published reports was to decrease or hold the antimetabolite but the impact of this strategy is unclear. Given that the pathogenesis of COVID-19 involves an exaggerated host inflammatory response that can be dampened by immunosuppression, the practice of routinely reducing immunosuppression, in the setting of viral illness, may need to be re-examined. In our series, we only held mycophenolate mofetil in one patient (Case 1), and this was in the setting of severe neutropenia and not due to concern for worsening of COVID-19 disease.

Our program is one of the largest pediatric heart transplant programs in the country, actively following hundreds of patients. Since the pandemic started, we have maintained frequent telehealth checks with the majority of them. Other than the four presented in this report, no other patient has manifested symptoms or tested positive for COVID-19. This may be because of our transplant patients and their families' efforts at self-quarantine, meticulous hand hygiene, and mask use. This behavior by no means eliminates the possibility that more patients have mild/asymptomatic infection but it is encouraging that patients have not presented with severe disease to date, nearly three months into the pandemic in our area. Given what we know about advanced age being the most prominent risk factor for severe COVID-19 disease in the adult population,[11,12] it is not surprising that our young patients had mild manifestations. On the other hand, most heart transplant recipients, even in pediatrics, have comorbidities such as hypertension, diabetes, and kidney disease that have been associated with more severe disease in adults.[9] One would expect that these comorbidities account for higher acuity in our population, but we did not observe that in these few cases we encountered. This may be due to the fact that their age is protective and overcompensates for their other risk factors but it really remains a speculation, given the limited number of patients.

To our knowledge, this is the first report of presentation and short-term outcomes of COVID-19 in pediatric and young adult heart transplant recipients. As we continue to gather data on the disease, it will certainly be beneficial to collaborate with other high volume centers to gain better insight on clinical course and optimal management of this disease in the young, immunocompromised patient. The question of whether reducing immunosuppression upon diagnosis of the viral infection is beneficial remains unanswered and at this point should be individualized. Longer-term follow-up will be necessary to determine the consequences of our actions as we continue to gain experience treating young heart transplant patients with COVID-19.

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