

Harlequin Syndrome in A Young Adult with Multi-System Inflammatory Syndrome Post COVID-19

Lerner RK^{1,7*}, Shilo N^{2,7}, Lotan D^{3,6}, Belinson V⁴, Kogan A^{5,7}, Pessach IM^{1,7}, Haviv Y^{6,7}, Mayan H^{2,7#} and Kassif Y^{5,7#}

¹Department of Pediatric intensive care, The Edmond and Lilly Children's hospital, Sheba Medical Center, Tel Hashomer, Israel

²Department of Internal Medicine E, Sheba Medical Center, Tel-Hashomer, Israel

³Leviev Heart Center, Sheba Medical Center, Tel-Hashomer, Israel

⁴Department of Internal Medicine C, Sheba Medical Center, Tel-Hashomer, Israel

⁵Department of Cardiac Surgery, Sheba Medical Center, Tel-Hashomer, Israel

⁶Intensive Care Unit, Sheba Medical Center, Tel-Hashomer, Israel

⁷Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

*Corresponding author:

Reut Kassif Lerner,
Department of pediatric intensive care,
The Edmond and Lily Safra Children's Hospital,
Sheba Medical Center,
Tel Hashomer, Israel,
E-mail: reutkl@gmail.com,
reut.kassif@sheba.health.gov.il

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Haim Mayan, Yigal Kassif. These authors contributed equally to this manuscript.

1. Abstract

COVID-19 patients have a heterogeneous disease course; it may be asymptomatic or cause only mild symptoms, while immunologic complications resulting in cytokine storm syndrome may also occur. Hereby, we present a young patient with cardiogenic shock and multi organ failure, suggesting Pediatric Multi-System Inflammatory Syndrome (MIS-C), which developed myocardial dysfunction that led to cardio-respiratory arrest, therefore required ECMO support. Whilst on ECMO, the patient stabilized very quickly however suffered from an acute event of severe hypoxemia and brain injury, possibly secondary to Harlequin syndrome. He was therefore converted to VA-V ECMO, and then to VV ECMO once the heart recovered completely, and managed to wean off ECMO support.

2. Introduction

The rapid spread of Coronavirus disease 2019 (COVID-19) caused

by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to a global pandemic, with infected individuals of all ages residing in almost every country in the world. At the time of writing this case report, the World Health Organization reported more than 20 million global cases of confirmed COVID-19 with nearly 800,000 deaths [1, 2].

In adults, COVID-19 is typically characterized by severe interstitial pneumonia and hyper-activation of the inflammatory cascade. In children, the respiratory involvement appears to have a more benign course, with almost no fatalities reported in this age group and only 2% of cases described in patients under age 20 [1, 3, 4].

Starting in March of 2020 there have been an increasing number of reports of an outbreak of Kawasaki-like illness following coronavirus infection. Pediatricians have identified children with symptoms ranging from gastrointestinal manifestations to a severe inflammatory systemic disease with myocarditis and shock [1, 7]. The Kawasaki-like disease described is a rare condition, probably

affecting no more than one in 1000 children exposed to SARS-CoV-2. This estimate is based on the limited data from few case series [1, 5, 6]. This presentation of multisystem inflammatory syndrome in children associated with SARS-CoV-2 (MIS-C) may lead to serious and life-threatening illness in previously healthy children and adolescents [7].

The cause of Kawasaki disease remains unknown; however, earlier evidence suggests that an infectious agent triggers a cascade that causes the illness. The most accepted hypothesis supports an aberrant response of the immune system to one or more unidentified pathogens in genetically predisposed patients [1, 5, 6, 8].

In the past 20 years, viruses of the coronavirus family have been proposed as possibly implicated in the pathogenesis of Kawasaki disease. As SARS-CoV-2 being a particularly virulent strain, it might be able to elicit a powerful immune response in the host. The mechanism for the Kawasaki-like disease described might represent post-infectious inflammatory syndrome, which might be antibody or immune-complex mediated [1].

3. Case Report

Here we present a case report of a 26-year-old man, previously fit and well, who presented to the emergency department with fever and gastro-intestinal (GI) complaints. The differential diagnosis was lymphadenitis or GI infection and he was admitted to the internal medicine department for further management. Over the next 72 hours, the patient has deteriorated, suffered from ongoing dyspnea, chest pain and acute renal failure. CTA revealed bilateral new lung infiltrates. Full laboratory, rheumatologic and infectious investigations were inconclusive including negative PCR for COVID-19. He was then semi-electively intubated for Broncho alveolar lavage (BAL), when he started deteriorating rapidly. He became severely hypoxemic, required high-pressure ventilation, showed hemodynamic instability, and was treated with high dose vasopressors. Three hours later, the patient was in deep cardiogenic shock and subsequently went into pulseless electrical activity. Three full rounds of cardiopulmonary resuscitation were required; therefore, he was commenced on VA E-CPR (veno-arterial extracorporeal cardiopulmonary resuscitation). Additional tests revealed IgG positive serology for COVID-19 and the BAL was also positive for COVID-19, therefore he was transferred to the corona intensive care unit. More laboratory tests revealed very high troponin levels, which raised the possibility of myocarditis. Lymphopenia, thrombocytopenia, hyperbilirubinemia and high transaminases, high D-dimer, procalcitonin and CRP, severe metabolic acidosis – were all suggestive of severe inflammatory storm. All lab results are shown in (Table 1). ECG was abnormal with ST-T changes and small complexes. Echocardiography showed ejection fraction (EF) of 5-10%. The patient received steroids, methylene blue, broad-spectrum antibiotics, blood products, and

intravenous immunoglobulin (IVIG). He was later established on continuous hemofiltration due to renal failure. Over the next 24-48 hours, he became more stable; Echo showed improving cardiac contractility with EF 45%. The patient had spontaneous breaths, normal pupillary response, as well as cough and gag. On day 5 of VA-ECMO, the patient suffered an acute event of severe upper body hypoxemia, his pupils became dilated, which correlated to a drop in the brain NIRS (Near-infrared spectroscopy). He was then commenced on full treatment for brain edema, whilst correcting hypoxemia with maximal effort on the ventilation side. Brain CT was not performed due to his unstable condition. Assuming that the reason for this acute event was low perfusion of oxygenated blood to the brain due to high cardiac output opposing the ECMO flow, he was started on β -blockers, and the ECMO configuration was changed to VA-V ECMO. Later it was changed to VV. The patient gradually stabilized and we managed to wean him off ECMO. However, he continued to demonstrate severe anoxic brain injury, and unfortunately passed away.

Table 1: laboratory result

Laboratory test	day 0 (admission)	Day 3-4 (collapse)	Day 8 (severe hypoxic episode)
WBC (K/microL)	5.98	16.54↑	23.22↑
Hemoglobin (M/microL)	13.72	9.82↓	9.06↓
Platelets (K/microL)	126↓	145	56↓
Lymphocytes%	5.7↓	10.5↓	5.5↓
Urea (mg/dl)	19	59↑	192↑
Creatinine (mg/dl)	0.78	3.17↑	3.41↑
SGOT (AST) – (IU/l)	63↑	961↑	196↑
SGPT (ALT) – (IU/l)	133↑	386↑	278↑
GGT (IU/l)	34	79↑	311↑
Alkaline phosphatase (IU/l)	87	129↑	210↑
LDH (IU/l)	268	2030↑	2938↑
Bilirubin total (mg/dl)	1.25↑	3.39↑	8.03↑
CPK total (IU/l)	481↑	806↑	8287↑
CRP	266↑	276↑	98↑
Troponin I (ng/l)	146	7216↑	1643↑
D-dimer	-	68491↑	19062↑
Fibrinogen (mg/dl)	643↑	333	234
Ferritin (ng/ml)	606↑	17187↑	1863↑
INR	1.17	2.95↑	1.05
Procalcitonin (ng/ml)	3.85	269↑	182↑

4. Discussion

The above case report of a young patient who presented with abdominal pain and high fever, later deteriorated to cardiogenic shock and inflammatory storm, is suggestive of Pediatric Multi-System Inflammatory Syndrome (MIS-C) which has been previously described in the literature. The differential diagnosis for this patient also included cardiomyopathy/myocarditis, or cardiogenic shock secondary to sepsis. As the patient stabilized very quickly and cardiac function improved dramatically within 48 hours, the diagnosis of hypoxic cardiogenic shock cannot be ruled out. Basic brain stem function was preserved.

On day 5 of ECMO support, the patient had an acute event of severe hypoxemia and brain injury, possibly secondary to Harlequin syndrome (Figure 1). He was therefore converted to VA-V ECMO, and then to VV ECMO once the heart recovered completely. The patient finally stabilized and weaned off ECMO support, but unfortunately, suffered from severe anoxic brain damage and did not survive.

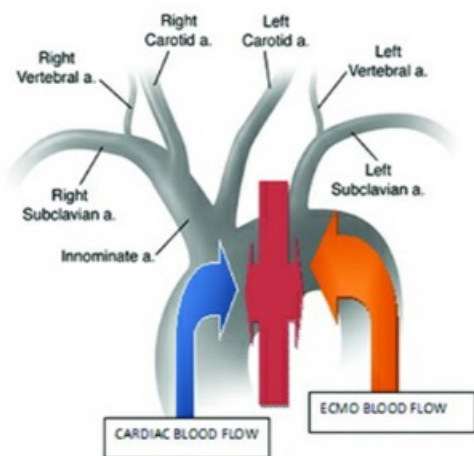


Figure 1: Harlequin syndrome

*adopted from Rupprecht et al.

Various genetic mutations may constitute a risk factor for a severe disease course and occurrence of cytokine storm in COVID-19. Once immunologic complications like cytokine storm occur, anti-viral treatment alone is not enough and should be combined with appropriate anti-inflammatory treatment, such as corticosteroids and IVIG, as our patient received [1, 9].

As previously described in 2005 by Ruiz-Bailen et al. [10], reversible myocardial dysfunction may be due to myocardial stunning following global myocardial ischemia during cardio-respiratory arrest, in the absence of acute or previous coronary artery disease. Experimentally, a correlation has been found between the degree of ventricular dysfunction and the duration of the resuscitation, in our patient -3 prolonged resuscitations and a result of EF of 5-10%. The young age of our patient, precludes previous ischemic

heart disease as the cause for the myocardial dysfunction.

Harlequin syndrome is described in patients on VA ECMO, where differential oxygen saturation is observed between the upper and lower parts of the body. In VA ECMO, the upper body hypoxia occurs due to compromised arterial return, while the heart function is recovering, and the lungs are still poorly functioning. The arterial jet flows upstream in the aorta and may meet the antegrade flow generated by the left ventricle. Depending on the amount of native cardiac function, the location of the interface between antegrade and retrograde flow will vary, but will usually be in the aortic arch. It is a rare complication; however, it can be as high as 8.8%. Therapeutic options of Harlequin syndrome consist of relocation of the arterial cannula into the right subclavian artery or aorta, or converting to central VA-ECMO. It can also be solved by converting the system into a VA-V setting, as in this case described above [11, 12].

5. Conclusion

COVID-19 patients have a heterogeneous disease course; it may be asymptomatic or cause only mild symptoms, while immunologic complications resulting in cytokine storm syndrome may also occur. Therefore, a patient who presents with cardiogenic shock and multi organ failure should be considered to be suffering from post-inflammatory syndrome. Furthermore, the development of myocardial dysfunction might also be post cardio-respiratory arrest and the need for prolonged resuscitation. For patients who require ECMO support, the decision should be made between VA-ECMO and VV-ECMO, according to the cardiac function, whilst performing careful monitoring for myocardial improvement.

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