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CASE REPORT
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Hemadsorption as a Treatment Option for Multisystem Inflammatory Syndrome in Children Associated With COVID-19. A Case Report

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Multisystem Inflammatory Syndrome in Children (MIS-C) *associated with COVID-19* is characterized by hypercytokinemia leading to overwhelming inflammation. We describe the use of a hemadsorption device as part of the supportive treatment for cytokine storm.

Keywords: hemoadsorption, inflammatory multisystemic syndrome, myocardial injury, cytokine - immunological terms, SARS-CoV-2

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INTRODUCTION

There are significant clinical and immunological data describing the clinical consequences of MIS-C as an immunopathogenic illness. Therefore, a key intervention would be the control of the cytokine storm (1–3).

CASE REPORT/CASE PRESENTATION

We present a 17-year-old male with a history of fever, dyspnea, diffuse chest and abdominal pain, and generalized rash on day 13 of COVID-19 molecular diagnosis and within the first two weeks of clinical presentation. The polymerase chain reaction (PCR) test for COVID-19 was negative, while the serum IgG levels were present. The patient presented a rapid deterioration, which evolved into cardiogenic shock with biventricular dysfunction (30% left ventricular ejection fraction on transthoracic echocardiography) and acute hypoxemic respiratory failure. The primary differential diagnoses were sepsis of bacterial origin (including staphylococcal and streptococcal toxic shock syndromes), other systemic viral infections (adenovirus, enterovirus), acute abdomen, Kawasaki disease, drug hypersensitivity, autoimmune or autoinflammatory diseases, and hemophagocytosis.

The blood cultures were negative for bacteria and fungi. The initial evaluations for hemophagocytosis and immunological or pharmacological-related causes were negative. Chest and abdominal CT imaging were performed. The patient had CT findings of ileitis. Blood analyses showed a hyperinflammatory profile (**Table 1**). He required orotracheal intubation and rescue maneuvers for severe hypoxemia. The final diagnosis was narrowed into acute myocarditis secondary to MIS-C (diagnosis of exclusion). The patient fulfilled the Royal College of Pediatrics and Child Health of the United Kingdom (RCPCH-UK) criteria for MIS-C associated with COVID-19 (4). He received empirical treatment with intravenous (IV) amoxicillin-clavulanic, IV methylprednisolone (2mg/kg/day), IV immunoglobulin (1g/kg/d) for three days, and cytokine hemadsorption by a 24-hour treatment with Cytosorb®. The patient received the adjunctive therapy with hemoadsorption during the first 24 hours of ICU admission. Informed consent for the initiation of the hemoadsorptive technique was requested from the patient's family. He required vasopressor and inotropic support that was retired after 4 days of treatment (**Table 1**). Focused bedside transthoracic ultrasound showed progressive improvement of biventricular global function after hemoadsorptive treatment. The patient was discharged from the ICU on day 5 and discharged from the hospital on day 20. In the subsequent outpatient follow-up, the patient has fully recovered to his baseline level of activity, and no chronic sequelae have been detected.

DISCUSSION/CONCLUSION

In critically ill adult patients, hyperinflammation plays a significant role in the pathophysiology of multiple organ failure (5, 6). The clinical and laboratory features of hyperinflammation, timing from SARS-CoV-2 infection onset, and similarities in the disease pattern among adults with COVID-19, support the hypothesis that MIS-C results from immune-mediated injury triggered by SARS-CoV-2 infection (7). Currently, there are clinical, microbiological, and immunological data describing MIS-C as a novel immunopathogenic illness (8, 9).

Several official organizations, such as the Centers for Disease Control of the United States (CDC), the World Health Organization (WHO), or RCPCH-UK, have tried to define the general characteristics of MIS-C. However, there is no consensus regarding case definition and clinical management (10, 11).

Treatment includes IV immunoglobulin (12), high-dose IV corticosteroids, and control of hypercytokinemia. For the control of hypercytokinemia, the use of interleukin-1 (IL-1) (13) antagonist (anakinra) and interleukin 6 (IL-6) receptor antagonist (tocilizumab) (14) has been suggested. Recent studies in SARS-CoV-2 patients have shown that these antagonists do not improve mortality (15–19), and tocilizumab has been associated with an increased risk of nosocomial infections (20). However, these studies have been performed in adults, and their results should not be extrapolated to younger patients, such as ours.

Regarding infection risk, hemoadsorption treatment sessions are of short duration. Thus, the risk of infection of intravascular devices used for extracorporeal support seems low, particularly in critical care units where preventive measures are widely implemented. Short- or mid-term hemoadsorption-associated infections have not been described.

The extracorporeal cytokine hemoadsorption device (Cytosorb®) (21) was approved for its use in critically ill COVID19 patients (22, 23). The cartridge has been previously used for cytokine storm-related hyperinflammatory conditions (24) and has been subject to many recent studies (25). Cytokine storm encompasses a heterogeneous group of disorders characterized by life-threatening hyperinflammation, and may be present in non-infectious pathologies (26). We hypothesized that cytokine removal may ameliorate cytokine storm and provide clinical benefits in our patient´s clinical scenario. Previous experience published in sepsis shows that cytokine hemoadsorption is a safe procedure with no associated adverse effects (27).

In our patient, hemoadsorption achieved a safe and rapid reduction of cytokine levels. From a clinical point of view, fast improvements in shock and multiorgan dysfunction parameters were observed. He had no adverse effects associated with the technique, vasopressor support was reduced by more than 80%, and organic dysfunction, measured by the SOFA score, improved from 14 to 6 points in 24 hours. Cytokine levels decreased

TABLE 1 | Evolution of the vasopressor support, clinical anf laboratory values.

	PreHA	PostHA	48h ICU admission	60h ICU admission	Reference values
CRP/ (mg/dL)	30.68	36.25	20.2	19.98	0.03-0.50
Ferritin (ng/mL)	399	619	400	394	25.00-400.0
IL-6 (pg/mL)	3457	47.8	41.92	28.13	0.00-4.30
IL-10 (pg/mL)	90.3	9.24	6.9	7.88	0.00-7.80
CD25s (pg/mL)	16969	16596	12038	14914	400.00-2000.00
DD (ng/mL)	902	1368	603	725	0.00-243.00
SOFA	14	6	2	2	–
P/F	60	400	432	–	–
S/F	–	–	–	326	–
NAD (µg/kg/min)	0.8	0.08	0	0	–
DBT (µg/kg/min)	2	2	0.2	0	–

The hemoadsorption (HA) technique was performed within the first 24h of ICU admission. CRP, C-reactive protein; IL-6, interleukin-6; IL-10, interleukin-10; CD25s, interleukin-2 soluble-receptor; DD, D-dimer; SOFA, Sequential Organ Failure Assessment (points); P/F, PaO_2/FIO_2 ratio; S/F, $SpO2/FiO_2$ ratio; NAD, noradrenaline; DBT, dobutamine; HA, hemoadsorption (duration 24h).

considerably, and the rest of the acute phase parameters were progressively reduced in the following hours once the hyperinflammatory stimulus was attenuated. The downstream effects (C-reactive protein, soluble CD25 [sCD25], and ferritin levels) are minimal since it mainly reduces acute phase mediators that can be eliminated by hemoadsorption. However, such mediators are reduced after the attenuation of the cytokine storm. Ferritin as an example, is not removed by hemoadsorption, thus we understand the rise of ferritin as corresponding to the evolution of the base process; the ascent occurs in the first 24 hours and decreased rapidly from this moment on due to the treatment implemented.

As this is a case report, causality cannot be confirmed, particularly when considering the other treatment interventions required (e.g., corticosteroids, immunoglobulins, and multiorgan support). However, there was a close temporal relationship between the initiation of hemoadsorption and the reductions in cytokine levels and clinical improvement. IL-6 and IL-10 levels were significantly reduced in 24 hours. Rapid improvements in respiratory function (PaO_2/FiO_2 ratio improved from 60 to 400), shock and organ dysfunction parameters (SOFA score improved from 14 to 6 points) were documented 24 hours from initiation of therapy. The patient´s favorable clinical evolution should be attributed to all therapeutic interventions, though the rapid clinical improvement may be attributed to cytokine elimination by hemoadsorption, as it has not been described as a pharmacological effect of corticosteroids or immunoglobulins. MIS-C requires multifactorial treatment. Although corticosteroids and immunoglobulins could have progressively and ultimately modulated inflammation, we consider hemoadsorption responsible for the rapid improvement in respiratory, hemodynamic, and organ dysfunction. Consequently, we consider hemoadsorption a potential adjunctive therapy in patients with MISC-C severe multiorgan dysfunction. Our results must be confirmed in larger studies.

Our case report has several limitations. We report an isolated clinical case, and a cause-effect relationship cannot be confirmed. However, we are aware of the critical role cytokine storm-control had in the rapid reduction of multiorgan support in our patient, despite having received conventional treatment. Impressively, he was discharged from the ICU on day 5 of admission. The cytokine measurements are those included in our institution´s clinical analyses panel.

Beyond being the first to describe the potential usefulness of hemoadsoption for MIS-C associated with COVID-19, the main strength of this case report relies on the rapid control of hyperinflammation observed by cytokine hemadsorption. In combination with conventional treatment, cytokine hemoadsorption can achieve early clinical improvements. This case report supports the effectiveness of hemoadsorption in hypercytokinemia control, though larger and controlled studies are essential to draw any meaningful conclusion.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

We complied with the guidelines for human studies and our research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. Subject gave their written informed consent to publish their case. Information revealing the subject's identity is to be avoided.

AUTHOR CONTRIBUTIONS

Substantial contributions to the conception or design of the work. Drafting the work or revising it critically for important intellectual content. Revising the manuscript critically for important intellectual content. All authors contributed to the article and approved the submitted version.

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