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Refractory Multi-Inflammatory Syndrome in a Two Weeks Old Neonate with COVID-19 Treated Successfully with Intravenous Immunoglobulin, Steroids and Anakinra

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Case Report
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Abstract

Background: World Health Organization (WHO) and other Health officials alert clinicians about a rare but severe inflammatory condition seen in children and linked to Corona Virus Disease 2019(COVID-19). The WHO is describing the condition as a multisystem inflammatory syndrome in children (MIS-C) and is recommending clinicians to report those cases to get a better understanding of the disease and clinicians can learn more.

Case Presentation: We are reporting the clinical course of the youngest case of COVID-19 related MIS-c; a two-week-old term neonate with COVID-19 infection and features suggestive of MIS-C, managed with intravenous immunoglobulin (IVIG), pulse steroid, and interleukin-1 inhibitor (Anakinra). By reviewing the literature, our baby is the first neonatal case who has been diagnosed with MIS-C.

Conclusion: COVID-19 infections in pediatrics are likely to present with a mild course; however, some may develop a hyper-inflammatory syndrome. Pediatricians should be aware of such presentation, the clinical course, the management modalities, and inform parents and caregivers about common signs and symptoms. Anakinra may consider as effective second agent in (IVIG and steroid-refractory pediatric cases).

Keywords: Neonatal COVID-19; SARS-Cov-2; Multisystem Inflammatory Syndrome of Children MIS-C; Pediatric Multi-System Inflammatory Syndrome PIMS

Abbreviations: HMC: Hamad Medical Corporation; HGH: Hamad General Hospital; COVID-19: Corona Virus Disease 2019; MIS-C: Multisystem Inflammatory Syndrome of Children; SARS-Cov-2: Sever Acute Respiratory Syndrome Corona Virus-2; WHO: World Health Organization; CDC: Centers of Diseases Prevention and Control-United States; RCPCH: Royal College of Pediatrics and Child Health-United Kingdom; PCR: Polymerase Chain Reaction; CBC: Complete Blood Count; WBC: White Cell Count; PCT: Procalcitonin; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation

Rate; LFT: Liver Function Test; NT-Pro BNP: Natriuretic Peptide Test; IL-6: Interleukin-6 Test; IL-1β: Interleukin 1 Beta; IVIG: Intravenous Immunoglobulin; Mg: Milligrams; Kg: Kilograms; ARDS: Acute Respiratory Distress Syndrome; NYSDOH: New York State Department of Health; ECDC: European Centre for Disease Prevention and Control.

Introduction

The clinical course, progression, and outcome of COVID-19 disease in pediatrics are milder and less severe than adult. They have lower rates of hospitalization and death as well [1-5]. Multi-system inflammatory syndrome in children (MIS-C), which is called pediatric multi-system inflammatory syndrome (PMIS) as well, is a newly recognized, possibly serious illness in children that is recently connected to COVID-19 infection. It appears to be a late complication of COVID-19 infection, even though some patients were labeled with this complication without testing positive for sever acute respiratory syndrome corona virus -2(SARS-CoV-2). Since March 2020, many of the UK and USA pediatricians and in many other countries in Europe during the coronavirus disease 2019 (COVID-19) pandemic, started to notice and report children presenting with fever and multi-system inflammation. The presentations were variable and included children who had features similar to those of Kawasaki disease, streptococcal / Staphylococcal toxic shock syndrome, Sepsis, probably in relation to SARS-CoV-2 infection [6-9]. Children who were critically ill needed intensive care unit admission [10].

To date, there are suggestions for diagnosing MIS-C based on case definition. World Health Organization (WHO), Centers for disease control and prevention of United States (CDC-USA) and Royal college of pediatrics and child health of United Kingdom(RCPCH-UK) proposed the symptoms of (persistent fever, Kawasaki like features and dysfunction of one or more organs), laboratory investigations showing signs of inflammation, as the main criteria to diagnose MIS-c [7,11].

Case Presentation

A two weeks old female baby, born spontaneously at full term with a birth weight of 3.2kg in the maternity unit at the hospital. She presented with neonatal fever and admitted to pediatrics inpatient in May 2020. Initial laboratory workup was done to rule out neonatal sepsis, and she had full sepsis workup done for her, included Lumbar Puncture, at the third day of admission she was checked for COVID-19 polymerase chain reaction (PCR) and found to be positive, though she did not have any contact with COVID-19 patient, both parents were screened with a nasal swab after her diagnosis and were negative. After that, she was shifted to pediatrics COVID-19 inpatient area in the main and only pediatrics COVID-19 institution and stayed there for nine days, where her clinical and laboratory conditions were strictly observed.

The baby was continuously spiking high-grade fever throughout her stay with baseline tachycardia; although she clinically and hemodynamically continued to be stable, her inflammatory markers were increasing (Tables 1 & 2), declaring a state of acute inflammation. She was conscious alert and active and did not have any respiratory symptoms and was having normal oxygen saturation on room air despite her chest x-ray showing bilateral lungs infiltrates (pneumonitis), when consulted pulmonologist advised for starting Antibiotics. However, her clinical examination only revealed mild hepatosplenomegaly with no skin rash, lymph nodes enlargement, or Kawasaki disease signs. She had multiple laboratory investigations aiming to discover the source of infection and the degree of inflammation.

Complete blood counts (CBCs) were showing lymphocytic leukocytosis with (total WBC 31600/µL), she had normocytic normochromic anemia with hemoglobin level dropping up to (8.7 g/dL), With mild thrombocytopenia of (124 x10^3/µL). Her C-reactive protein (CRP) was steadily rising from (6 to 84mg/dl), hypoalbuminemia (23g/l), hyponatremia (127mEq/L), and her lactic acid reached up to (6.4mmol/l) with normal PH and Kidney function. Liver functions showed a mild increment in liver transaminases, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), were doubled with normal coagulation (Table 2). All her cultures came back negative with CSF cell count showing increased RBC counts -deemed traumatic, and we decided to do an ultrasound head, which came to be normal.

The baby was screened again after first positive COVID-19 PCR on two consecutive days, eighth & ninth, and the results were negative COVID-19 PCR and other respiratory virus's nasal swabs (Table 2). When she continued to be febrile and tachycardic with increasing inflammatory markers and a drop in her hemoglobin, Baby was transferred to the main hospital in the pediatrics inpatient unit in an isolation room to complete the investigation as multisystem inflammatory syndrome of children (MIS-C) was suspected. Her ferritin level markedly raised (1773 ug/l), Troponin, and her Natriuretic peptide test (pro-BNP) were both increased (Table 2), cardiac wise she had an Echocardiogram which was done twice, and it was showing normal coronary arteries and contractility. With her persistent tachycardia and low hemoglobin, the primary physician and upon pediatrics hematology consult both agreed to transfuse her packed red blood cells. On the same day, pediatrics rheumatologist reviewed the baby and advised to start (IVIG two grams per kilogram per dose) (Table 1), along with Aspirin high dose of 75 mg per dose every 6 hours per day, Same day

she was given one dose of Dexamethasone (Table 1) then commenced on Methylprednisolone as pulse steroid (30mg/kg) once daily for three days with tapering dose over the next days (Table 1). After IVIG infusion, the baby continued to have high inflammatory markers; then, it was decided by a multidisciplinary team to admit her to the pediatric intensive care (PICU) unit to give the second line therapy, immunomodulatory therapy (Anakinra) as a refractory case.

Dose of Anakinra was (2mg/kg) loading dose (Table 1), followed by a continuous infusion of (0.02ml/kg/hour) [12]. Efficacy and safety-wise were the reasons to give continuous infusion, not subcutaneous (SC) injection, as there is no recommended dose for this age group as SC injection. She received Anakinra on day17 of illness and completed 9 days then was stopped. She was kept on antibiotics (Piperacillin/Tazobactam) (Table 1) for presumptive pneumonitis for 10 days and as pediatrics infectious diseases services were involved early, Baby was not started on any other COVID-19 medications, and especially she did not have any respiratory symptoms.

Baby was then re-spiked low grade fever on day 34 of admission and after around 24 hours from discontinued Anakinra , her primary team decided to give her a second dose of Intravenous immunoglobulins IVIG, unfortunately no laboratory investigations were taken before starting it, then was observed for three more days with inflammatory markers went back to normal . She was discharged home after total of five weeks of hospitalization in good general condition; she was then followed up by pediatric rheumatology and pediatric cardiology team along with general pediatrics. Echocardiogram was also repeated and continued to be normal.

Medications Received	Dose	Route	Duration
Anakinra	2mg/kg bolus then continuous	IV continuous infusion	For 9 days
	Infusion of [(0.02ml/kg/hr.)		Started day 11 of illness
Ampicillin	150mg/kg/day	IV Q8hours	For 6 days started day1 of illness
Aspirin	80mg/kg/day	PO Q8hours	For 3 days started day 12 of illness
Cefotaxime	150mg/kg/day	IV Q8hours	For 9 days started day 1 of illness
Cholecalciferol	1000 IU/day	PO once daily	Started day 14 of illness
Dexamethasone	0.2 mg/kg/dose	IV Q6hours	For two doses started day 11 of illness
Enoxaparin	2mg	Subcutaneous Q12hours	For 3 days
			Started day19 of illness
Esomeprazole	1mg/kg/day	PO once daily	Started day 11 of illness
Intravenous immunoglobulin (IVIG)	2gram/kg/dose	IV over 12 hours	for two doses
			1st at day 9 of illness 2nd at day 29 of illness
Methylprednisolone	30mg/kg/day	IV once daily	For 3 days
Metronidazole	35mg 30mg/kg/day	IV Q8hours	For 2 days
	05-07-2005		Started day 7 of illness
Phytomenadione	1 mg	Once daily	For 3 days
			Started day 14 of illness
Piperacillin/Tazobactam	100mg/kg/dose 5- 16/5	IV Q8hours	For 11 days
			Started day 9 of illness
Prednisolone	2mg/kg/day	PO once daily	Started day14 of illness with weaning dosage

Table1: Management course.

Day of	WBC	Hb	PLT	CRP	ESR	Ferritin	Fibrinogen	D.Dimer	Pro-BNP	Troponin-T	Albumin	Triglycerides	Lactic acid	Procal citonin	AST	COVID-19	Other Important labs or events
illness	103/ul Normal 5-19	g/dl Normal 11-16.5	103/ul Normal 200-500	mg/dl Normal <10	mm/hr Normal <10	ug/L Normal 6-430	g/l normal 1.3-3.3	mg/L FEU Normal 0-0.44	g/ml (normal<125pg/m	ng/L Normal 3-10	gm/l Normal 38-54	mmol/l Normal <1.7	mmol/l Normal 1.1-3.5	ng/mL	U/L Normal 0-79	PCR swab	
D1	9.4	14.5	311	6.1							34		3.5	0.23	33		CSF WBC 19 RBC 500(59%l)Full septic cultures werenegative-respiratory panel was negative Started on IV antibiotics (ampicillin cefotaxime)
D3																Positive	
																	Sterile pyuria urine WBC 17
D5	11.4	11.9	151	50							34		2.8	0.41	52		
D7	13.5	10.7	124	75.8							31		4.4	0.51	78		
D10	27.9	10.1	158	84.5							31		6.4	0.53	152	Negative	Tazocin started Respiratory viral panel was negative Us head was normal and abdomen Us showed splenomegaly
D12	31.6	8.7	161			1,773	1.1	11.46	1,518	17	23				93	Negative	Received IVIG,PRBC,+ dexamethasone for2 doses Methylprednisolone pulse steroid started anti-inflammatory dose aspirin ECHO is normal VwF was 418% Vitamin D was 12 ng/ml(normal >30 ng/ml) ANA, ant-DsNA negative ANA-CTD positive CK 55 normal GGT was 51 U/L normal (15-232) ammonia 145 umol/l (normal up to 95)

D14	16.9	10.9	242	40.4	18	1,69	0.96	5.82	5,555		23		4.8	0.23	42		Started vitamin K for 3 days Prophylactic Enoxaparin started for 3days
D15	19.1	11.1	246	21.7		851	0.91	4.49	3,528	12	24			0.17	32		Repeated ECHO is normal
D17	21.3	11.6	251	37.4		825			569	29	29			0.14	28		Started on Anakinra (interlukin-1 inhibitor) infusion
D19	16.2	10.2		28		975	2.58	3.27	486	20	24				23		
D21	13	9.6	302	15		1,084	2.62	16.57	482	36	25				31		
D22	16	9.7	388		37	1,371	3.22	5.49		43	29				39		
D23	13.6	8.6	356			1,201	2.44	3.56	429		26				37		
D24	14	9		4		1,076		3.55	544		28				48		
D26	13.6	9.3	424			1,031	2.44	3.15	694	97	31				49		
	14.7	9	440				2.58	2.97	568	95	29	3.2			48		
D28	11.4										32	3.4			45		
D30																	
D31		8.9															
D32																	Anakinra infusion stopped (completed 9 days)
D34	7.6	8.8	388	14.6	137	598	2.3	2.28			34		2.1		52		Spiked low grade fever Received second dose of IVIG
D37	10.5	8.9	500	12.6	101	338		1.74			34				38		Repeated ECHO is normal

Table 2: Laboratory values.

Discussion

Our case report involving hospitalized neonatal case, two weeks old with MIS-C, which is the youngest case in State of Qatar and according to our knowledge through all the literature as well. Our case fulfils the criteria of Pediatric multisystem inflammatory syndrome associated with COVID-19 and the case definition that has been recommended by different sources such as New York State Department of Health (NYSDOH) and European Centre for Disease Prevention and Control (ECDC) [7,11]. Only one suspected neonatal case was reported in a research study group, involved with the age Group (0 to 5 years of age) in New York. The baby presented at 14 and 28 days of age with fever and left breast cellulitis. Echocardiogram Showed good ventricular function and unremarkable coronary arteries. Two molecular tests for SARS-CoV-2 were negative. The discharge diagnoses were cellulitis, and shock [12].

As in different studies, our MIS-C case followed the peak of infection by almost two weeks, which support that this syndrome is probably a post infectious inflammatory process related to Covid-19 [12,13]. A profound inflammatory response resulting in Acute Respiratory Distress Syndrome (ARDS) and multi-organ failure seems to be an essential component of the critical illness associated with COVID-19. Some critically ill cases will manifest shock and cardiac dysfunction, probably due to cytokine storm (CS) resulting from the host response to viral infection [14]. Interleukin -6 (IL-6) & Interleukin 1 beta (IL-1β) levels are elevated in patients with severe COVID-19; however, fewer data have been reported to date in COVID-19 patients regarding IL-1β [15]. High inflammatory markers like C-reactive protein (CRP) level and other abnormal parameters that mentioned in the presentation of our case explain that this inflammatory syndrome is probable mediated by IL-6. Different immunomodulatory therapies have been discussed and tried to manage the inflammatory response such as Tocilizumab and Anakinra

[9,16].

Management remains difficult; most cases have been treated as atypical Kawasaki Disease with additional supportive care as needed. Considering the rarity and complexity of the syndrome, it would be essential to establish and coordinate to guide diagnosis, treatment, and follow-up. Our case received IVIG, Pulse steroid, then Anakinra. The decision regarding giving Anakinra not Tocilizumab for our baby was initiated, Since Anakinra is used to treat patients with neonatal-onset multisystem inflammatory disease (NOMID) [17]; it is known to be safe for use in neonates, infants as well as children and adults. Moreover there was no specific dose and safety profile regarding Tocilizumab use in this age group. Till more data are available, the routine use of Tocilizumab and Anakinra in patients with severe or life- threatening COVID-19 is not recommended. Nevertheless, the use of these medications may be considered, in consultation with pediatric Infectious Diseases, Immunology, and pediatric Rheumatology in conjunction with the patient's primary team in patients with severe disease and clinical deterioration. There are ongoing Clinical Trials, for example, NCT02735707, NCT04339712, NCT04330638, NCT04324021. A multicenter clinical trial in the United States is being designed to test the use of Anakinra in adults with COVID-19.

Conclusion

SARS-CoV2 infections in pediatrics are likely to present with a mild course; however, some may develop a hyper-inflammatory syndrome. Pediatricians should be aware of such presentation, the clinical course, the management modalities, and inform parents and caregivers about common signs and symptoms. Anakinra may consider as effective second agent in (IVIG and steroid-refractory pediatric cases).

Declarations

- **Ethical Approval:** This case report received Ethical approval from the medical research committee at Hamad Medical Corporation (MRC-04-20-601).
- **Consent for Publication:** Waiver of signed informed Consent for this publication was obtained.
- **Availability of Data and Materials:** The data sets during and/or analyzed during the current study available from the corresponding author on reasonable request.
- **Declaration Competing Interests:** Authors declare that they have no competing interests and no potential conflicts of interests with respect to the research, authorship, and /or publication of this article.
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