BRIEF REPORT

MULTISYSTEM INFLAMMATORY SYNDROME IN AN INFANT WITH NEGATIVE SARS-COV-2 RT-PCR AND ANTIBODIES

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ABSTRACT:

Since the declaration of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic in March 2020 by the World Health Organization (WHO), there has been an emergence of a new syndrome termed multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19. MIS-C is defined by the presence of fever, systemic inflammation and multiorgan dysfunction in association with SARS-CoV-2 infection or COVID-19 exposure. Knowledge of this syndrome's presentation and pathophysiology is constantly evolving as more cases are reported in the literature. This case identifies a 3-month-old patient who tested negative for SARS-CoV-2 antigen, reverse transcriptase polymerase chain reaction (RT-PCR) and antibodies but qualified for MIS-C diagnosis. To the best of our knowledge and through extensive research at the time of diagnosing and reporting this condition to the healthcare authorities, we report the youngest pediatric patient with MIS-C diagnosis. We document this case to contribute to further understanding the variable manifestations of MIS-C and the importance of early diagnosis and treatment with intravenous immunoglobulin (IVIG).

INTRODUCTION

A pandemic was declared by the WHO in March 2020 of COVID-19 due to the development of a novel coronavirus designated SARS-CoV-2.[1] The clinical course of the disease in the majority of pediatric cases has been asymptomatic or mild.[2-5] In more recent literature, it has become apparent that some children may develop a more severe clinical course with a MIS-C. This syndrome is defined as systemic hyper inflammation with fever and multiorgan dysfunction in relation to COVID-19 exposure.[6] The average age of MIS-C patients is eight-years-old but typically ranges from 1-14-years-old.[7] Clinical presentation is variable, with most cases reporting significant gastrointestinal symptoms, cardiac disease, skin rash, conjunctivitis, absent or mild respiratory symptoms and oral mucous membrane changes.

Many of the cases reported in the literature identify MIS-C with overlapping symptoms of Kawasaki disease (KD) or toxic shock syndrome (TSS).[8-15] KD and MIS-C share several common symptoms, including skin rash, lymphadenopathy, strawberry tongue and an elevation of inflammatory biomarkers. These similarities likely suggest that MIS-C exhibits the same excessive inflammatory cytokine production in response to an infectious trigger observed in KD. However, the exact pathophysiology is still under investigation. Previous reports have shown that MIS-C differs from KD by the older age of onset, abdominal symptoms and left ventricular systolic dysfunction.

RT-PCR has been effective in identifying active COVID-19 cases and the more recent antibody tests may aid in identifying cases with related post-infectious complications. There was a question of whether MIS-C is a primary complication of infection with SARS-CoV-2 or a post-infectious complication; however, it either occurs 2–4 weeks following exposure or is associated with positive antibody markers, which supports the conclusion that it is likely a post-infectious complication.[16] This brief report intends to describe the clinical presentation and successful treatment of an infant diagnosed with MIS-C.

CASE PRESENTATION

A three-month-old African American male with no significant past medical history presented to urgent care with a two-day history of fever and rash, accompanied by abdominal pain, dry cough, diarrhea and lethargy. Physical examination was benign other than an erythematous rash on the face and chest with papules on the torso and axilla. The patient was up-to-date on immunizations with no recent exposure to sick contacts. He was diagnosed with a

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viral illness and viral exanthem with a possible allergic component. The parents were instructed to continue supportive care at home.

The patient presented to the emergency department the next day with a high-grade fever that did not resolve with multiple doses of acetaminophen. The mother reported associated symptoms of cough and a new bilateral eye discharge with eye redness. Vital signs showed a temperature of 103.3°F and a heart rate of 195 beats per minute. Physical examination showed bilateral conjunctivitis and purulent eye discharge. No rash was evident at this visit. He was treated with acetaminophen and, once stable, discharged home on supportive management for a viral syndrome.

The patient returned to the emergency department on day four of his illness with unresolved fever, abdominal pain, diarrhea, conjunctivitis and irritability. The mother reported a significant decrease in the patient's oral intake and urine output. Physical examination showed an ill-appearing, nontoxic infant with 10% loss of body weight over two days, evidence of severe dehydration and diffuse abdominal tenderness. Lungs were clear to auscultation with no respiratory distress. The patient received two normal saline fluid boluses 20 mL/kg each without resolution of the tachycardia. The patient was then admitted to the general pediatric floor for fever of unknown origin and dehydration with COVID-19 precautions.

The patient's parents denied the patient having any recent illnesses or sick contact but reported a positive COVID-19 case at the father's job at a steel plant. The mother stays at home with the patient and his six older sisters, who were reported to be well and healthy with no recent illnesses. None of the family members had recently been tested for COVID-19.

Goal-directed investigation for MIS-C through testing aimed at:

1. Evidence of current or recent infection with SARS-CoV-2

2. Laboratory markers of inflammation

3. Multisystem organ involvement

4. Exclusion of other etiology and diagnosis

During the patient's hospital stay, a full sepsis workup was completed and empiric antibiotics, which included ampicillin, ceftriaxone and vancomycin, were given. Laboratory studies were notable for leukocytosis with neutrophil predominance, thrombophilia, lymphocytopenia, hypoalbuminemia, elevated inflammatory markers, elevated D-dimer, hypertriglyceridemia, sterile pyuria and cerebrospinal fluid (CSF) pleocytosis (Table 1). An echocardiogram was performed to assess cardiac function and any coronary artery involvement and revealed normal results. Gallbladder ultrasound was ordered to rule out hydrops of the gallbladder, which showed gallbladder wall thickening (Figure 1) with pericholecystic and perisplenic edema. Chest radiography was normal. Microbiological investigations included blood culture, stool culture, conjunctiva secretion culture, CSF fluid culture with gram stain, FilmArray Respiratory Panel, FilmArray Meningitis/Encephalitis Panel, Epistein Barr Virus DNA PCR, and SARS-CoV-2 RT-PCR, antigen, IgG and IgM were all negative.

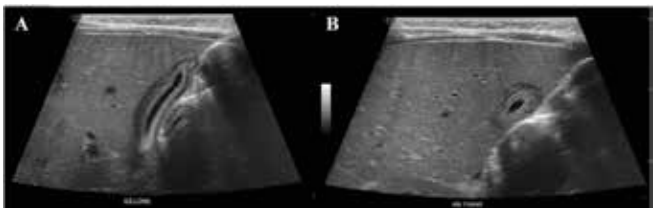
TABLE 1:

Lab	Value	Reference Range	Unit
WBC count	**21.1**	6.0–17.5	x 103/uL
Hemoglobin	10.6	9.5–13.5	g/dL
Hematocrit	31.7	29.0–41.0	%
Platelets	**472**	130–400	x 103/uL
Segmented neutrophils	**86**	16–60	%
Lymphocyte count	**8**	19–50	%
Creatinine	0.3	0.3–0.6	mg/dL
BUN	10	5–27	mg/dL
BUN/Creatinine ratio	33	8–23	-
Albumin	**2.5**	2.7–4.8	g/dL
AST	**19**	22–58	IU/L
ALT	14	11–39	IU/L
CRP	**24.90**	0.00–0.60	mg/dL
ESR	**82**	0–15	mm/hour
Procalcitonin	**0.81**	Non-ICU patients: < 0.25 bacterial infection unlikely ≥ 0.25 bacterial infection likely ICU patients: < 0.50 bacterial infection unlikely ≥ 0.50 bacterial infection likely	ng/mL
D-Dimer	**3.54**	0.00–0.46	ug/mL
Ferritin	222.6	22.0–322.0	ng/mL
Lactate Dehydrogenase	292	140–304	IU/L
Troponin	<0.006	0.000–0.040	ng/mL
Triglycerides	**129**	30–100	mg/dL
Urine WBC	**10**	0 –8	Per hpf
CSF WBC	**14**	0–5	Per hpf
CSF RBC	5	<1	/cmm
CSF glucose	63	50–80	mg/dL
CSF protein	35	15–45	mg/dL

(WBC: white blood cell, RBC: red blood cell, BUN: blood urea nitrogen, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, AST: aspartate aminotransferase, ALT: alanine aminotransferase, CSF: cerebral spinal fluid)

FIGURE 1:

Longitudinal (A) and transverse (B) view of gallbladder demonstrating gallbladder wall thickening



On day seven of symptoms, because the patient was not clinically improving and met all of the criteria for MIS-C diagnosis, he received a 2 g/kg dose of IVIG. The patient showed significant clinical improvement and laboratory values began to normalize. CRP decreased markedly. High-dose acetylsalicylic acid (ASA) of 80 mg/kg/day was given until he remained afebrile for 48 hours. The patient was discharged (Figures 2 and 3) home to continue ASA of 5 mg/kg/day.

FIGURE 2:

Fading of skin rash

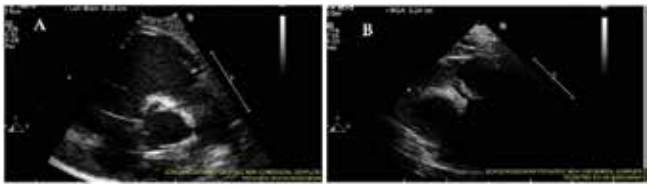
FIGURE 3:

Absence of oral mucosal inflammation

Four days after discharge, the patient returned to his pediatrician with a fever of 100.7°F, persistent cough, congestion and irritability. Laboratory investigation showed an elevated white blood cell count of 30.9 x 103/uL. Repeat echocardiogram showed initial signs of coronary artery dilation formation (Figure 4). He received a second dose of IVIG in addition to corticosteroids and continued high-dose ASA. The patient responded well to treatment, fever subsided and laboratory values returned to normal limits.

FIGURE 4:

Repeat echocardiogram showing Initial signs of coronary artery dilation. (A) Left main coronary artery 0.25 cm (normal 0.11-0.23), (B) proximal right coronary artery 0.24 cm (normal 0.08-0.19), left anterior descending artery 0.19 cm (normal 0.08-0.14).



DISCUSSION

MIS-C is a clinical diagnosis made by ruling out plausible alternative diagnoses and fulfilling the criteria defined by the U.S. Centers for Disease Control and Prevention (CDC) or the WHO.[6,17] When this patient was admitted to the hospital, he was on day four of his fever. Laboratory values supporting signs of inflammation included lymphocytopenia at 8%, hypoalbuminemia of 2.5 g/dL, elevated CRP of 24.90 mg/dL, elevated ESR of 82 mm/hour and elevated D-dimer of 3.54 ug/mL. Multisystem organ involvement included the gastrointestinal system with diarrhea, the dermatological system with a rash and the neurological system with aseptic meningitis. A full sepsis workup provided there was no explanation for another source of infection or fever.

After an extensive review of published MIS-C cases, it is important to note this case differs from others due to the lack of positive RT-PCR or antibody tests. Although the patient had no known sick contacts and no family members diagnosed with COVID-19, we suspect there may have been unknown exposure due to potential asymptomatic carriers and the continued increasing number of cases in the area.[18] Two studies have shown that asymptomatic carriers of COVID-19 infection are likely to produce an infection in close contacts that are also asymptomatic.[19, 20] In conjunction with the evidence that children typically experience asymptomatic or mild symptoms during active SARS-CoV-2 infection, this would support our hypothesis that if anyone in contact with our patient over the prior four weeks had an asymptomatic COVID-19 infection, that unknown exposure is likely for this case. We hypothesize that the negative SARS-CoV-2 results seen in this patient could be attributed to several factors, including high false-negative rates in the RT-PCR test and failure of detection in the antibody test. A study of 1,330 confirmed COVID-19 cases with RT-PCR revealed that the false-negative rate for SARS-CoV-2 RT-PCR was highly variable, with the highest rate of 67% within the first five days of exposure and the lowest rate of 21% on day eight after exposure.[21] IgM and IgG antibodies against SARS-CoV-2 have increased sensitivity after one week of symptom onset.[22] This

highlights the importance of how the timing and sensitivity of these tests may affect the accuracy of the results. Although SARS-CoV-2 antibody testing has been shown to have high sensitivity and specificity, researchers are still discovering more about antibody response characteristics. Immune responses to SARS-CoV-2 can vary from person to person and currently are not well studied in infants due to the low incidence of COVID-19 cases in the younger population.

Our patient also lacked the criteria necessary to meet complete KD or TSS, unlike many other reported cases. A cohort study of Kawasaki-like disease cases in the Bergamo province reported a dramatic increase of new cases of KD with an increased incidence of nearly 30-fold over the past five years.[14] The region observed for this study had the highest rate of COVID-19 infection and death in Italy. A retrospective cohort study of 33 pediatric patients diagnosed with MIS-C in Cohen Children's Medical Center revealed 64% fulfilled the complete criteria for KD.[23] Our patient met one out of five criteria for KD, although he had rapid clinical improvement when treated with KD protocol, which includes IVIG and ASA. The successful treatment, similar manifestations and occurrence after exposure to an infectious agent may suggest that KD and MIS-C may have similar pathophysiology. Although the older average age of onset in MIS-C and the high occurrence of gastrointestinal symptoms and incidence of left ventricular dysfunction warrants further investigation for other factors that may contribute to the severity and nature of the syndrome.

CONCLUSION

The number of cases of MIS-C associated with COVID-19 is expected to increase as the SARS-CoV-2 pandemic progresses. Our understanding of the underlying pathophysiology and potential manifestations will improve with additional reports and research. This is a pediatric case in an infant that meets MIS-C criteria with negative SARS-CoV-2 testing, which was successfully treated with IVIG. Our study's limitations include the absence of COVID-19 diagnosis due to two negative RT-PCR tests, a negative antigen test and negative IgG and IgM tests. There also was no presence of COVID-19 illness in the family which may reduce the likelihood of exposure in this patient. The timing and sensitivity of available SARS-CoV-2 tests may affect the accuracy of the results. Therefore, unknown exposure to COVID-19 should not exclude MIS-C from the differential diagnosis.

Given that the understanding of MIS-C is still evolving, it is important to closely follow potential MIS-C patients as the physical examination findings do not appear simultaneously but rather evolve over several days. Increased index of suspicion and early decision to initiate intensive care is critical in successfully treating MIS-C. In this case, treatment with two doses of IVIG was successful. If MIS-C goes undiagnosed, the deterioration can be quite rapid and severe, resulting in a significantly increased mortality rate. This case highlights the importance of high clinical suspicion for MIS-C and early treatment benefits with IVIG.

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