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Research Article

Staph Hominis in Overlapping Presentation of MIS-C, Kawasaki-Like-Syndrome, and Toxic-Shock-Syndrome in COVID-19 PCR Negative Child

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ABSTRACT

Background: Multisystem Inflammatory Syndrome in Children (MIS-C) is a serious condition in which some parts of the body including the heart, blood vessels and other systems become inflamed. Inflammation typically includes swelling, often with redness and pain. Many, but not all, children with MIS-C test negative for a current infection with the virus that causes COVID-19. Often toxic shock syndrome can manifest with a similar presentation in children, which usually results from toxins produced by Staphylococcus aureus. We present the case of 10-year old boy tested negative COVID-19 twice, and presented to our Pediatrics-ER with high grade fever, generalized body rash, loose motion, cough, and poor oral intake for 2 days.

Case Report: 10 years old boy who had been tested negative for SARS-CoV-2 infection, was presented with his mother (who's a nurse in a clinic) to the ER with high grade fever, generalized body erythema, and erythematous macular rash. He also had cough, loose motion, and poor oral intake for the last 2 days. A real-time polymerase chain reaction test was negative for the second time, and blood culture identified staph Hominis, dividing the underlying etiology into two differentials.

Conclusions: The etiology of MIS-C/Kawasaki-Like-Syndrome is unclear, a likely hypothesis of an infectious agent as a trigger for inflammatory reaction, among those agents are Staphylococcus, and Corona-Virus. The MIS-C is a life threatening condition, and delaying of IVIG administering is fatal, Coronary Aneurysm could end with. MIS-C presentation could resemble TSS caused by Staphy Hominis, particularly in those who at risk of contracting (HAI) hospital acquired infections. Further studies shall be conducted on the role of such normal skin flora could play in triggering MIS-C in children who are genuinely COVID-19 negative, since a follow up contact, 4 weeks post discharge revealed a negative result of the child's COVID-19 Ig-G Antibody Serology Test.

Categories: Infectious Disease; Immune-mediated Disease; Pediatrics; Dermatology

Keywords: MIS-C; COVID-19; KD; TSS

Patient: Male, 10-year-old

Final Diagnosis: MIS-C vs. Staph Sepsis

Symptoms: high grade fever, and erythematous macular rash

Medication: The MoH of Saudi Arabia Protocol of Treatment for MIS-C (IVIG, Prednisolone, Enoxaparin Sodium, and Ceftriaxone) + Acetylsalicylic.

Clinical Procedure: None

Specialty: Pediatrics

Objective: Unknown etiology

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INTRODUCTION

Multisystem Inflammatory Syndrome in Children (MIS-C) is a serious condition in which some parts of the body such as the heart, blood vessels, kidneys, digestive system, brain, skin or eyes — become inflamed. Inflammation typically includes swelling, often with redness and pain.

Many, but not all, children with MIS-C test negative for a current infection with the virus that causes COVID-19. Yet evidence indicates that many of these children were infected with the SARS-CoV-2 in the past, as shown by positive antibody test results. An antibody test with a positive result means that the child's immune system developed blood proteins (antibodies) that fought the COVID-19 virus. Sometime this blood test is the only indication that the child was ever infected. MIS-C shares some of the same signs and symptoms as another condition called Kawasaki disease; which mainly affects children under 5 years of age. It causes inflammation in the walls of blood vessels, particularly those that supply blood to the heart muscle (coronary arteries). Researchers are working to figure out if the two conditions are related or not [1]. Often toxic shock syndrome can be manifest with a similar presentation in children, which usually results from toxins produced by Staphylococcus aurous (staph) bacteria, but the condition may also be caused by toxins produced by group a streptococcus (strep) bacteria. TSS can affect anyone, men, postmenopausal women, and children. Risk factors include skin wounds, surgery, and the use of tampons and other devices, such as menstrual cups, contraceptive sponges or diaphragms [5]. This report presenting a case of 10-year Filipino boy tested twice negative COVID-19, and presented to our Pediatrics-ER with high grade fever, generalized body rash, loose motion, cough, and poor oral intake for 2 days and overlapping clinical and laboratory findings with the three differential diagnoses.

CASE REPORT

10 years old boy who had been tested negative for SARS-CoV-2 infection, was presented with his mother (who's a nurse) to the ER with high grade fever, generalized body erythema, and erythematous macular rash (Figures 1-4

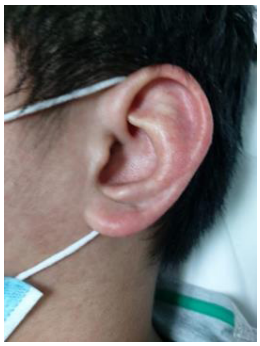

Figure 1: Erythematous and macular rash spreading in the face and neck of the patient, more prominent in the ears.

He also had cough, loose motion, and poor oral intake for the last 2 days. The patient's medical history shows no clue of probable exposure to SARS-CoV-2, completed vaccination history, and no dental or surgical intervention in the last 8 months. However, the fact that his mother is a medical nurse in a clinic during pandemic, reserve the possibility of virus contraction. The boy's parents have not experienced any symptoms during the prior period of their

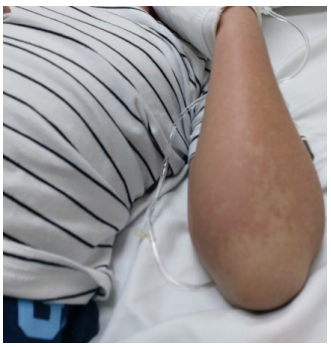

Figure 2: Erythematous rash spreading in the upper limbs of the patient.

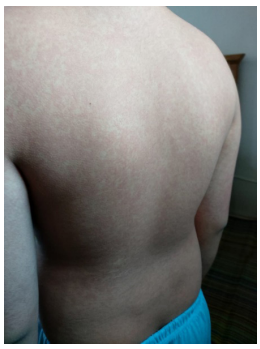

Figure 3: Erythematous rash with macules spreading in the back of the patient.

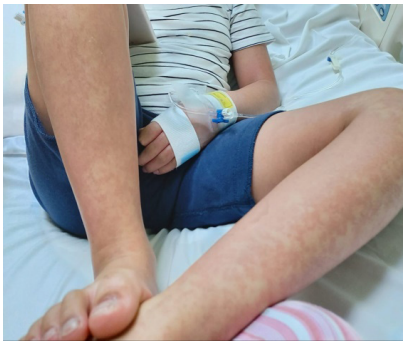

Figure 4: Erythematous macular rash spreading in the lower limbs of the patient.

child illness. After solving technical issues led to the delaying of the admission for 2 days and a course of Azithromycin taken from another clinic, where the condition was misdiagnosed as Pharyngitis; the boy's mother reported that his temperature had soared; bowel habits had changed, and mild cough presence in the preceding 2 days in association with a loss of appetite and the emergence of generalized erythematous rash, which was suspected as drug-eruption rash due to the Azithromycin intake. On clinical examination, the patient had his vitals as follow: Temp: 38.6° C, RR: 24/min, HR: 98/bpm, BP: 110/55 mm Hg, O2: 98% and hi weight: 45 Kg, height: 149 cm.

The patient was admitted as Fever with Rash for Investigation. The on-duty pediatrician registrar found that the patient had a congested

throat, with strawberry tongue, and generalized erythematous rash. No neurological symptoms were reported. Baseline laboratory tests and sepsis screening were performed to assess inflammation indices, the possibility of sepsis (Table 1). Contact precaution was set, and dermatology was consulted, in which the specialist responded as: Viral Exanthem for antihistamine. As the second day hematic and blood chemistry were repeated, no significant difference was detected ; but the inflammatory markers were reported critical; especially D-Dimer, LDH, and Ferritin; other chemistry and screening tests such as parasitic infection were negative (Table 2).

Test type		Value (Range)	
CBC with platelets	**Result**	**Unit**	**Normal ranges**
WBC	4.09 "LO"	10^9/L	4.5-11
NE%	66.9	%	40-75
LY%	19.2 "LO"	%	20-55
LY#	.785 "LO"	10^9/L	1-5
HGB	126	g/dl	115-160
PLT	215	10^9/L	150-450
Chemistry	Result	Unit	Normal Range
CRP (Quantitative)	26.02 "HI"	mg/dl	0-5
ESR	35 "HI"	mm/hr.	0-10
Procalcitonin serum	1.77 "HI"	mg/ml	<0.5: low risk of sepsis >2.0: high risk of sepsis

Table 1: Sociodemographic characteristics of the sample.

Test Type		Value (Range)	
CBC With Platelets	**Result**	**Unit**	**Normal Ranges**
WBC	2.64 "LO"	10^9/L	4.5-11
HGB	131	g/dl	115-160
PLT	196	10^9/L	150-450
Lab Haematology	Result	Unit	Normal Ranges
D-Dimer	3.59 "HI"	ug/ml	Less than 0.50 (Negative)
ESR	49 "HI"	mm/hr.	0-10
Chemistry	Result	Unit	Normal Range
Ferritin	229.23 "HI"	mg/ml	7-140
LDH	497 "HI"	U/L	125-220

Table 2: Inflammatory markers show critical results.

Despite the fact that the serology test for COVID-19 antibody is not available in our facility; at this point as the inflammatory markers were reported high, and correlated with the clinical signs and symptoms of the patient, a diagnosis of MIS-C was made, the patient was transferred to airborne isolation room, a second COVID-19 swab screening test was ordered, and an echocardiography consultation was requested.

The MoH of Saudi Arabia Protocol of Treatment for MIS-C was started as follow: [IVIG (2g/kg over 12 hrs.), Prednisolone (40 mg PO OD*10 days), Enoxaparin Sodium (0.5 mg/ kg BID S.C), and Ceftriaxone (50 mg/ kg OD*5days)]. After the completion of 48 hrs, the real-time Polymerase Chain Reaction (PCR) testing for SARS-Cov-2 nucleic acid on nasopharyngeal swab reported negative; after it was conducted according to the guidelines provided by the manufacturer. Later, the cardiology-pediatrician reported a normal heart, no evidence of carditis. CXR reported normal, and the patient was placed in regular room.

The laboratory tests were repeated every 48 hours to monitor the inflammation indices and white blood cells count. The patient experienced some pyrexia during the IVIG transfusion, and later some spikes of fever the next 2 days, which was treated with IV Acetaminophen.

The course of MIS-C treatment was augmented with multivitamins, and vitamin D; in addition, the patient dose of Ceftriaxone was adjusted to (100 mg/kg) as the lab reported gram positive blood culture. ECG was conducted and yield normal findings. Bleeding profile was done, due to three different moderate epistaxis episodes to the patient in the 5th, and 6th day of admission. However, positive history of spontaneous epistaxis was recorded. Laboratory investigations showed: normal cardiac enzymes (BNP, CKMB). Enoxaparin was discontinued and Acetylsalicylic Acid 5 mg/ kg daily dose was started.

A dramatic response to the treatment, in particular the IVIG; was observed clinically and laboratory, since the rash regressed, and the inflammation indices declined; for instinct, LDH (318) from (497), Ferritin (190) from (366), CRP (15.3) from (27), Procalcitonin (0.71) from (1.77), D-Dimer (1.76) from (3.5), However, PLT count kept dropping to (169) from (196). Upon the completion of one week of admission, IV Fluids was discontinued, and the patient tolerates his regular diet orally. Blood culture and sensitivity reported Staph Hominis (Table 3). In correlation, the patient general condition was good, afebrile, good oral intake, and normotensive.

Blood Culture and Sensitivity Result: Staphylococcus Hominis.	Notes Staphylococcus Hominis is one of the skin floras, correlate clinically. Sometime it can cause nosocomial infection in immune compromised patients.
Antibiotic	**Isolate and Sensitivity**
Azithromycin	S
Doxycycline	S
Erythromycin	I
Oxacillin	R
Sulfamethoxazole/Trimethoprim (Bactrim)	S
Vancomycin	S

Table 3: Blood C/S identified staphylococcus hominis.

Continuing the same plan, a reduction of Ceftriaxone dose once again to 50 mg/kg and oral Azithromycin was ordered. Reaching day 10 of admission; the patient condition totally resolved, despite the increase in ESR (80), the patient was discharged home as MIS-C/ Kawasaki-Like-Syndrome vs. query Gram-Positive Sepsis, on aspirin for the next 6 weeks, and to follow up with pediatrics clinic after 5 days. Moreover, pediatric cardiologist clinic was scheduled as well in 3 and 6 weeks for echo.

DISCUSSION

During pandemic of COVID-19, Kawasaki-Like-Syndrome or Toxic Shock Syndrome manifestations cannot be attributed solely to underlying reason, without being linked to the MIS-C Post COVID-19; giving the fact that our case was reported negative for COVID-19 PCR test, two times, and the COVID-19 antibody serology is not available.

Kawasaki Disease is a clinical diagnosis reached by exclusion, and correlation of the characteristic presentation and lab findings, which basically characterized by symptoms in phases,

the significance of early diagnosis of Kawasaki or Kawasaki-Like-Syndrome is the early administration of Aspirin beside the IVIG as well, as early echocardiography and follow up to avoid life-long complication (e.g. coronary aneurysm). Symptoms usually appear in three phases; 1st phase: signs and symptoms may include: a fever that is often is higher than 102.2 F (39 C) and lasts more than three days, extremely red eyes without a thick discharge, a rash on the main part of the body and in the genital area, red, dry, cracked lips and an extremely red, swollen tongue, swollen, red skin on the palms of the hands and the soles of the feet, swollen lymph nodes in the neck and perhaps elsewhere, irritability.2nd phase: the child may develop peeling of the skin on the hands and feet, joint pain, diarrhea, vomiting, abdominal pain. 3rd phase: signs and symptoms slowly go away unless complications develop. It may be as long as eight weeks before energy levels seem normal again [6].

In our case, the child had high grade fever for >3 days, macular and erythematous generalized body rash except the genitalia, and barely two loose motions in the first 4 days of illness, no conjunctivitis, cheilitis, peeling or desquamation of the skin, no lymphadenopathy at all, and was not irritable.

However, the etiology of Kawasaki Disease or Kawasaki-Like-Syndrome is unclear, the most likely hypothesis being the responsibility of an infectious agent as a trigger for inflammatory reaction in particular genetic area at risk, leading to an inappropriate immunological reaction. Among the agents implicated is Staphylococcus producing super-antigenic toxins, and Corona-Virus. It can also complicate a COVID-19 infection [7]. The MIS-C is a life threatening condition, which might manifest in many patterns with a wide range of severity, delaying of IVIG administering is fetal, and Kawasaki-Like-Syndrome's life-long complications (e.g; Coronary Aneurysm) could end with [7].

We found Staph Hominis the isolated organism in the blood sample of our case has a role in TSS, despite the fact that it is considered a normal skin flora, and represent a high proportion of the contaminated sample.

Based on one study conducted in the US in 1998, Two hundred eighty-five blood isolates were tested, including 92 judged to represent true bacteremia and 193 judged to represent contamination most common species detected were Staphylococcus epidermis's, Staphylococcus Hominis, and Staphylococcus haemolyticus. These three species accounted for nearly 98% of the clinically significant isolates and 89% of the contaminants. The isolation of other species almost always represented contamination. However, identification of the three most common species did not help distinguish pathogens from contaminants [8].

According to issued study conducted in the US as well, 1986; Coagulase-negative staphylococci that produce Toxic Shock Syndrome Toxin 1 (TSST-1) or a Staphylococcal Enterotoxin or both were isolated from various sources. Coagulase-negative strains that produce TSST-1 alone or with enterotoxin A were the only staphylococci isolated from seven patients with toxic shock syndrome. Two other toxic shock syndrome patients had coagulase-positive staphylococci also, but only the coagulase-negative strains produced TSST-1[9]. Staphylococcus Hominis could be transmitted to the child-as (HAI) hospital acquired infection-from his mother's working environment, that caused sepsis/bacteremia, in which eventually manifested as TSS. Immunocompromised patients, the elderly and young children are usually more susceptible than others [2]. According to the CDC, some of the common nosocomial infections beside urinary tract infections, and respiratory pneumonia, are bacteremia, and skin infections [2].Based on a study conducted in neonatal intensive care unit; nosocomial spread of Staphylococcus Hominis subsp. novobiosepticus strain found causing sepsis; a several other Coagulase-negative staphylococci CoNS species are reported to cause disease in infants. Recently, a novel subspecies of Staphylococcus hominis, S. Hominis subsp. novobiosepticus (SHN), was isolated from blood cultures and other clinical specimens [10]. In addition, MIS-C manifestation could resemble the presentation of TSS caused by gram-positive Staphylococcus Hominis, particularly in those who at risk of contracting HAI, which is usually transmitted via healthcare workers, and in case of infection to bloodstream the most causative organism is coagulase negative staphylococci i.e staph hominis [11]. The fact of contracting the Staphylococcus Hominis bacteremia from frequent dental clinic visits was excluded in our report, since the patient's medical history identified his last visit to a dentist was 9 months ago. However, Staphylococcus Hominis ss novobiosepticus were identified in the water of dental unit reservoirs, according to bacteriological assessment study [12].

Hence, it was diagnosed as MIS-C (Kawasaki-Like- Syndrome) in the differentials, according to the CDC case definition [13]. Our case was treated according to the MoH of Saudi Arabia Protocol of Treatment for MIS-C [14]

However, overlapping MIS-C with TSS caused by gram-positive Staphylococcus hominis remains, especially when considering the (HAIs) hospital-acquired infections that would be contracted by his mother from her work place "a crowded prison-clinic". Moreover, it is very important to consider (SHN) Staphylococcus hominis strains as causative organism of nosocomial infections according to one study conducted in Brazil [3].

Finally, on follow up with the child's mother after 4 weeks from discharge, the result of COVID-19 Antibody Immunoglobulin-G Test was reported negative, which exclude the SARS-CoV-2 as triggering factor for the MIS-C, and strengthen the possibility of Staphylococcus hominies as the underlying cause.

CONCLUSION

The etiology of MIS-C or Kawasaki-Like-Syndrome is unclear, most likely an infectious agent triggered inflammatory reaction, and leading to an inappropriate immunological reaction, among the agents is Staphylococcus-toxins and Corona-Virus. MIS-C and TSS are life-threatening conditions, delaying of IVIG administering is fatal in both, and Kawasaki-Like-Syndrome's life-long complications (e.g.; Coronary Aneurysm) could end with. MIS-C manifestation could resemble the presentation of TSS caused by gram-positive Staphylococcus hominis, particularly in those who at risk of acquiring Hospital-Acquired-Infection/Bacteremia, which is usually transmitted via healthcare workers, to patient's bloodstream and usually the causative organism is coagulase negative staphylococci i.e. staph hominis. However, its isolation in laboratories could not help distinguish pathogens from contaminants, and further studies shall be conducted in the role of such normal skin flora triggering

MIS-C in children who are genuinely COVID-19 negative.

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DISCLOSURE

Human subjects: Written consent was obtained from all participants in this study.

Conflicts of interest: in compliance with the ICMJE uniform disclosure form, all authors declare the following: Payment/ services info: All authors have declared that no financial support was received from any organization for the submitted work.

Financial relationships: All authors have declared that they have no financial relationships at present or within the previous years with any organization that might have an interest in the submitted work.

Other relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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