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Case Report

The Eyes Doesn't See what Mind Doesn't Know (Multisystem Inflammatory Syndrome- Related to COVID19, In Adolescent Patients, MISC)

Salooma AL balushi[1]*, Salma AL khanjari[2], Mohammed AL Oraimi[3] and Suad Al Bulushi[4]

[1]*Pediatric Emergency Department, AL Nahdha Hospital, Sultanate of Oman*
[2]*Oman Medical Specialty Board (General Foundation Program), Sultanate of Oman*
[3]*Oman Medical Specialty Board Emergency Medicine Senior Resident, Sultanate of Oman*
[4]*Adult Emergency Department, AL Nahdha Hospital, Sultanate of Oman*

***Corresponding Author:** Salooma AL balushi, Pediatric Emergency Department, AL nahdha hospital, Sultanate of Oman.

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Abstract

MIS-c (multi-inflammatory syndrome, related to COVID-19) is not only children disease,it can occur in Adolescent and adult population.

CDC definition of MISC: An individual aged < 21 years presenting with fever (Of > 38 for >24 hrs.),with laboratory evidence of inflammation and evidence of clinically severe illness requiring hospitalization, with two or more organ involvement (cardiac, renal, respiratory, hematologic, GI, dermatologic, neurologic) and no alternative diagnosis and positive for current or recent SARS-CoV2 infection by RT-PCR, serology or antigen test or COVID exposure within 4 weeks prior to onset of fever.

Our patient is 13 years old young male, with no comorbid, presented with picture of persistent high grade fever, vomiting, poor oral intake, being lethargic, not responding to oral antibiotics. Found to have pericarditis, AKI (acute kidney injury), with high inflammatory markers. He was critically sick, with the need of inotropic support, oxygen supply and admission to ICU (Intensive care unit). Due to the lack of reported cases in our country of misc beyond pediatric ages this was not in our adult medical team consideration. Hence, it was crucial to report this case to highlight the challenges in diagnosing and treating MISC in adult patients.

Keywords: *Multi-Inflammatory Syndrome; COVID-19; Pediatric; Adolescent; Adult*

Introduction

As per WHO MISC is described in children and adolescent in association with SARS-co-V-2 infection. It is associated with inflammatory state and multi organ involvement. Significant proportion of patients have cardiac manifestation presenting as shock and need inotropic support. Myocardial dysfunction include ventricular impairment, valvular regurgitation, pericardial effusion and coronary artery abnormalities.

To consider MIS-C if the following criteria present, fever >3days and at least 2 of the following:

- Rash or bilateral non purulent conjunctivitis or mucocutaneous inflammation signs (oral, hands, feet).
- Hypotension or shock.
- Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities (including ECHO, findings or elevated troponin/NT-proBNP).
- Evidence of coagulopathy (By PT, APTT, elevated D-dimers).
- Acute gastrointestinal problems (diarrhea,vomiting,or abdominal pain).
- And: Elevated inflammatory markers like CRP, ESR or procalcitonin).
- And: No other obvious microbial cause of inflammation,including bacterial sepsis, staphylococcal or streptococcal shock syndromes.
- And: Evidence of COVID-19 (RT-PCR,antigen test,or serology positive), or likely contact with patient with COVID-19
- Consider this syndrome with children with features of typical or atypical Kawasaki disease.

Case summary

First ED visit

A 13 years old obese -81 kg- Omani male presented to the emergency department complaining of sore throat for 5 days and fever for 3 days. No previous health issues. Fever was not relieved when taking 500 mg Paracetamol at home. On presentation, he was febrile (40.5 C), heart rate of 106 beat per minute, blood pressure of 104/51, and the patients' oxygen saturation was above 96% on room air. The physical exam revealed congested throat, other systemic examinations were unremarkable. Lab values are shown in the following chart.

Hb	12 (N)
WBC	7 (N)
Neutrophil	6 (H)
lymphocyte	0.5 (L)
Na	128 (L)
platelet	139 (L)
CRP	220 (H)
Creatinine	89 (H)
Urea	6 (N)
blood C/S	pending

Table (1): laboratory results
(N=normal, L=low, H=high, C/S= culture and sensitivity)

His chest x-ray was unremarkable. The patient was provisionally diagnosed with tonsillitis and pneumonia and he was managed with IV Augmentin 1.2 g, 500 ml normal saline bolus, and IV paracetamol. On reassessment, the patient was feeling comfortable and hemodynamically stable. Thus, he was discharged home with 5 day-course of oral Augmentin, Paracetamol and Ibuprofen and he was advised to report back if any worsening or new symptoms.

Second ED visit

After two days, the patient presented back to ED with complains of un-subsiding fever and sore throat. In addition to that, he complained of pleuritic right-sided chest pain, nausea, poor oral intake, vomiting and watery diarrhea (without blood or mucus) for 3 days. He also reported dysuria and frequency from 5 days and lower abdominal pain for 1 day mainly occurs after episodes of vomiting which is relieved afterwards. He also recently noticed redness in both eyes but without eye discharge. He denied any flue, cough or SOB. No contact with any sick people. No known allergies.

Clinically, he was looking sick, dehydrated, not in respiratory distress. Vitally: mild fever (37.5), RR, HR and O2 saturation within normal limits. SBP was 170. The physical exam revealed congested eyes and throat, strawberry tongue, chest was clear, normal heart sounds with no murmurs, no rash or enlarged lymph nodes. Abdomen was soft, lax, and mild lower abdominal tenderness with negative rebound tenderness and negative rovsings sign. There was no lower limb edema. Laboratory results are shown in the chart below. VBG, RBS and urine microscopy were all normal (Table 2 and Figure 1).

WBC	13.5 (H)
Neutrophil	12 (H)
lymphocyte	0.4 (L)
platelet	95 (L)
CRP	347 (H)
Creatinine	166 (H)
Urea	14 (H)
troponin	104 (H)
Lactate	2.9 (H)
APT	33
ALT	103
ALP	115

Table (2): laboratory results

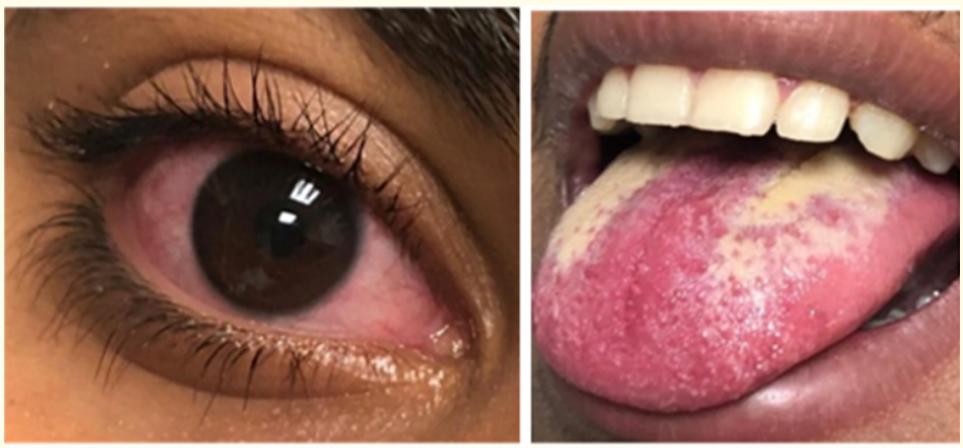

Figure 1: *Partial Kawasaki-Like Picture: Congested Eyes, Strawberry Tongue.*

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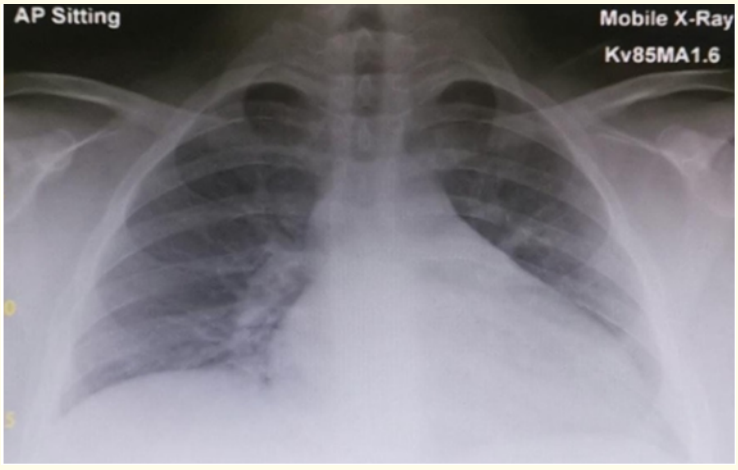

Figure 2: *Chest x-ray of second ED visit (ED=emergency department).*

The patient was provisionally diagnosed as septic shock, viral cause? With Acute Kidney Injury. Initial at presentation, the patient was managed with Normal Saline (NS) 500 ml, IV Metoclopramide 10 mg, IV Paracetamol 1 g. After noticing the high inflammatory markers, Ceftriaxone 2 g was started. One hour later, the patients' blood pressure started to drop as low as 77/35 and there was no adequate rise despite giving more NS boluses (total of 2.5 liters given). So ECG and urgent bedside ultrasound were requested and the patient was promptly started on Tazocin and Noradrenaline.

ECG showed a picture of myocarditis/pericarditis (sinus tachycardia, left ventricular hypertrophy with some Q waves, ST depression in lateral leads, and ST hump in lead v2).

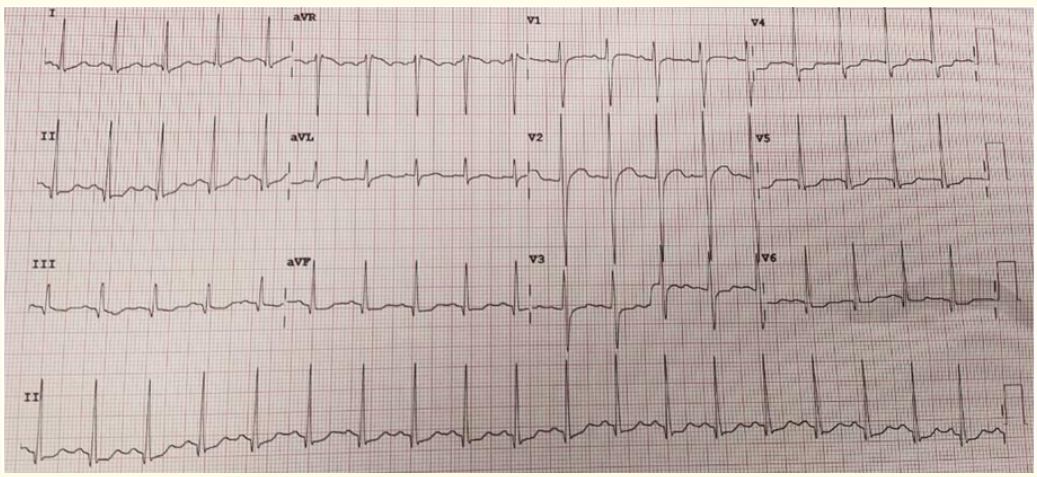

Figure 3: *Electrocardiogram.*

Ultrasound findings was reported as: " minimal free fluid in the pelvis, thin rim of pericardial effusion (4 mm), ejection fraction of 50%, appendix not visualized, mesenteric lymphadenitis (largest one is 11 mm), mild hepatomegaly, other organs unremarkable".

Other labs were added: ferritin of 3307 (H), D-dimer of 4.6 (H), fibrinogen of 8.6 (H), INR of 1.24 and due to highly suspicious case, the COVID swab was re-collected again and the result was released as positive. Blood and stool cultures were collected –pending-, HIV, hepatitis B and C antibodies were all nonreactive.

Patient was shifted from isolation room to COVID emergency resuscitation room. He was maintaining saturation on 2 L oxygen via nasal cannula and MAP on NA 0.1 mcg, tachypnic 30-40, on IVF maintanane and later IV Dexamethasone and Claxane were administered.

Intensive care unit

Next day, the patient was shifted to the Intensive care unit in another hospital, anesthesia was consulted for the need of intubation but they replied as "patient did not require intubation despite persistent tachypnea because he is maintaining saturation with three liters of oxygen via nasal cannula and ABG results were acceptable (pH 7.35, pCO2 37, pO2 97, HCO3 20, lactate 1.4, P/F ratio 248) with not very bad chest x-ray".

In the ICU, patient was covered with Tazocin but he was still spiking fever reaching up to 39.5, so Levofloxacin was added to the regimen. The patient was still sick and critical, tachypneic reaching 44 and requiring Noradrenalin 0.1 - 0.2 mcg. Infectious disease team within the hospital was consulted regarding the patient's condition and they advised to change Tozocin to Meropenum and Metronidazole with continuation of Levofloxacin.

Surgical review was taken to rule out any surgical abdomen and they didn't see any need for surgical intervention as the patient was not having abdominal complains. Abdomen was soft, no areas of tenderness, rigidity or guarding and the bowel sounds were present. Abdominal ultrasound showed minimal peritoneal fluid with mesenteric lymph nodes.

A suggestion from the referring Emergency department in the 1st hospital (with experience on MISC pediatric cases) raised the high possibility of patient having COVID 19 associated multisystem inflammatory syndrome especially that the patient was not improving with the current plan of management despite being on broad-spectrum antibiotics and negative cultures.

Thus, a multidisciplinary team meeting was conducted (including Intensive Care Unit consultant, Infectious Disease consultant, Internal medicine and Rheumatology consultant) to discuss the patient condition with the final decision that the patient is fitting the criteria of multisystem inflammatory syndrome with COVID-19 and so to start him on MIS-C protocol.

Pediatric Rheumatology expert opinion was taken and agreed to start on (MOH ICU protocol) for MIS-C treatment: Methylprednisolone 10 mg/kg as loading dose then to continue maintenance dose of 2 mg/kg once daily. IV Immunoglobulin 1g/kg infusion over 12 hours. Clexane 0.75 mg/kg BID (enoxaparin is favored over aspirin in the risk of venous thromboembolism with the use of IVIG).

Significant clinical improvement was noticed within one day after starting MIS-C treatment regimen; the patient fever subsided, inotropes was tapered down and stopped two days later, respiratory rate also improved and the patients' general condition became much better.

Cardiology was consulted to repeat echo which showed minimal pericardial effusion with normal cardiac contractility and no worsening changes compared to the previous echo. He also received daily mobilization and chest physiotherapy sessions with pruning 16 hours per day.

On further questioning, the family confirmed contact with COVID 19 positive case 6 weeks back and test was resulted as positive for the patient's mother, father and siblings. (See the chart below to correlate laboratory and clinical improvement with changing treatment regimen).

Medications Added	Augmentin IVF		Tazocin IVF NA 0.1	Tazocin Levoflox Clexane 8000 bid Dexa NA 0.2 3 L O2	Mero Metro Levo clexane600 0 bid MP IVIG NA .07	Ca/ vitD MP NA .02 1 L O2	Ca/v clexane MP NA stopped On RA	Ca/v clex MP	Ca/v clex MP	All Antibiotics stopped clex MP .	Ca/vitD aspirin Predni-solone
	First ED visit		second ED visit	Intensive Care Unit			General COVID ward				
2020	10/10	11/10	12/10	13/10	14/10	15/10	16/10	17/10	18/10	19/10	20/10
Vital Signs	T 40.5 RR 20 HR 106 MAP 68		T 37.5 RR 45 HR 135 MAP 55	T 39.5 RR 40 HR 140 MAP 54 (70 with NA)	T 39.8 RR 44 HR 120 MAP 62		T 37.4 RR 40 HR 95 MAP 70			T 37 RR 26 HR 90 MAP 75	
WBC	7		13.5	16	20		15			11	
Neutrophil	6		12	15						9	
lymphocyte	0.5		0.4	0.4						2.3	
platelet	139		95	91	132					285	
CRP	220		347	294	215		130			100	
Creatinine	89		166	139	75					5	
Urea	6		14	14	8					602	
Ferritin			3307							2.2	
fibrinogen			8.7								
D dimer			4.6	3.8	3.5		2.3				
troponin			104	130							
lactate			2.9								

Table 3: *Laboratory and hemodynamic improvement with changing treatment regimen. (IVF= intravenous fluids,NA=Noradrenalin,dexa=dexamethasone,Ca/v=calcium/vitamin. MP=methylprednisolone,levoflox=levofloxacin ,RA=room air, T=temperature. RR=respiratory rate,MAP=mean arterial pressure, HR=heart rate).*

General COVID ward

After being off ionotropic support, tolerating orally, mobilizing and improving inflammatory markers (see the figure above), he was shifted to the general ward. He stayed there for another four days. Antibiotics were stopped as all cultures came as negative. He was discharged home with tapering doses of prednisolone over 3 weeks, omeprazole for 8 weeks, calcium/vitamin D BID for 8 weeks, aspirin for 1 week. During his stay, complements levels were noted to be low so urgent samples of RF, ANA, dsDNA, ENA, RF, Anti CCP and ANCA were sent; and he was given a follow up appointment in rheumatology clinic for further evaluation for possible connective tissue disease/ systemic lupus erythematosus; and another appointment in cardiology clinic to repeat echocardiogram.

Discussion

The ministry of Health of Sultanate of Oman (MOH) case definition for MIS-C is:

A child presenting wit:

- Persistent fever more than 38 C, and laboratory evidence of inflammation by one or more markers (such as, neutrophilia, CRP, ESR, fibrinogen),
- Evidence of clinically severe illness requiring hospitalization, with single or multiorgan involvement (cardiac, renal, respiratory, hematologic, Gastrointestinal, or neurological), with additional features (like skin rash, conjunctivitis, mucus membrane changes, swollen hands and feet).
- No other possible alternative diagnosis, and
- SARS-CoV-2 infection confirmed by RT-PCR, serology, or antigen testing (or, negative SARS-CoV-2 test, with history of exposure to a suspected or confirmed COVID-19 case recently) [1].

Our patient, a previously healthy young 13 years male, who was considered as an adult according to the Omani classification (pediatric age less than 13 years while adult age starts from 13) met the above criteria with the exception of age.

The clinical features of our patient raised the suspicion of MIS-C-like illness. First, he was noted to have conjunctivitis and strawberry tongue with persistent fever for more than five days upon evaluation in the ED, which was suggestive of the Kawasaki like disease. Conjunctivitis has very rarely been reported in adults with COVID-19 [2], but multiple case series of MIS-C in the pediatric population have reported this clinical feature [2,3]. Additionally, our patient had profound GI symptoms leading to hypovolemia and Acute kidney injury (creatinine of 166), which was fluid-responsive initially but required inotrope support. While GI symptoms do occur in adults with COVID-19, they are typically less severe; by contrast, prominent GI symptoms are seen in many patients with MIS-C [5,6]. Finally, the respiratory status of our patient's was itself a feature shared by patients with MIS-C, who often lack intrinsic respiratory disease [2].

Other clinical characteristics were potentially compatible with MIS-C-like illness, including shock. Like many patients with MIS-C, our patient required treatment with vasopressors in the ICU; his shock was thought to be multifactorial including hypovolemic and cardiogenic. He had elevated troponin, but like many patients with MIS-C, his Echocardiogram showed finding like, minimal pericardial effusion with normal cardiac contractility [7].

Several other clinical features of our patient were less consistent with MIS-C as reported in the pediatric population. His profound acute kidney injury was not a feature described in most of MIS-C cases reported up to date [5]. Additionally, his neutrophilia and lymphopenia were more consistent with typical COVID-19 findings in adults, though they have been described in cases of MIS-C as well.

Conclusion

We describe an uncommon case of MISC-like illness in a young adult with COVID-19. MIS-C is an emerging and poorly understood clinical entity that has been described in children with COVID-19 and has overlapping features with Kawasaki's disease and Toxic shock syndrome. Children with MIS-C are increasingly treated with IVIG, aspirin, and steroids but it is not clear what if such clinical features in adults may warrant similar treatment approaches. Our patient was treated with IVIG and aspirin and improved without cardiac complications and inotrope was tapered down and stopped within two days.

Our case report emphasized the unfamiliarity of adult medicine about such possible presentations with the need of different treatment regimen and possible better outcomes. At least in our settings, we recommend the need of more open dialog (between adult and pediatric medicine) in the possible treatment regimens of such patients with no response to the traditional regimens especially in new unfamiliar disease entity as the covid-19 related illness.

Further research about COVID-19 in the young adult population is needed to better characterize the full range of clinical manifestations and current case definitions will need to be revised more frequently.

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