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RHABDOMYOLYSIS ASSOCIATED ACUTE KIDNEY INJURY IN SARS-COV2 MULTISYSTEM INFLAMMATORY SYNDROME IN CHILDREN

Paediatric Medicine

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ABSTRACT

BACKGROUND; Multisystem inflammatory syndrome in children (MIS-C) is defined by CDC as An individual aged <21 years presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); *AND* No alternative plausible diagnoses; *AND* Positive for current or recent Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) infection by Reverse Transcriptase Polymerase Chain Reaction (RT-PCR), serology, or antigen test; or (Corona Virus Disease 2019) COVID-19 exposure within the 4 weeks before the onset of symptoms.

CASE: We report an 11-year male who presented with the predominant feature of renal injury with gross hematuria and proteinuria along with features of multi-organ dysfunction treated with IV methylprednisolone and renal replacement therapy only. As per the reports available to date MIS-C can have acute kidney injury along with other features which rarely require renal replacement therapy.

CONCLUSION: Most MIS-C cases have mild kidney injury requiring supportive care only. MIS-C causing rhabdomyolysis and rapidly progressing renal failure is a rare presentation of COVID-19. MIS-C without coronaries involvement can be treated with high-dose steroids only.

KEYWORDS

Multisystem inflammatory syndrome in children (MIS-C), Rapidly Progressive Renal Failure (RPRF), Corona Virus Disease 19 (COVID-19), Rhabdomyolysis.

INTRODUCTION:

Corona Virus disease 2019 (COVID-19) was first identified in Wuhan province of china in December 2019 and was declared a pandemic by the world health organization on March 12, 2020. Since then the number of cases around the world are going up, India has seen close to 35 million cases across the country. Since the SARS-CoV-2 is a novel virus, understanding the pathogenesis and clinical presentation of the disease caused by it is still evolving.

MIS-C (Multisystem Inflammatory Syndrome-Children) is an established entity now and defined by CDC/WHO [1,2], the incidence of Acute Kidney Injury (AKI) in MIS-C ranges from-10-60%[3, 4] in different cohorts varying according to the severity of illness in respective cohorts. There is very limited information on children presenting with kidney injury and having COVID- 19.

CASE:

An 11-year-old fully immunized male presented to the hospital with a one-day history of fever along with severe abdominal pain, recurrent vomiting, and decrease urine output along with dark color urine. When has was attended to emergency room, he was conscious oriented but was screaming with abdominal pain. On examination, he has cold extremities, pallor, tachycardia, tachypnea, and low blood pressure (80/50mmHg) for age, sex, and gender. After fluid boluses up to 40ml/kg, his blood pressure did not improve and he becomes more confused. Inotropes adrenaline, noradrenaline, milrinone, and vasopressin were added as per need because of refractory shock, child was electively ventilated as per shock management protocol. Over the next 6 hours, the child passed less the 0.1ml/kg/hour of dark-colored urine. His lab reports showed deranged renal function and metabolic acidosis [table -I] so the decision to start renal replacement therapy was taken. The child was started on continuous renal replacement therapy with Continuous Veno-Venous Hemodiafiltration mode (CVVHDF) and which was continued for the next 96 hours. During further evaluation child was found to have hematuria nephrotic range proteinuria (Urine dipstick 4+), low complements C3, very high creatine kinase, high lactate dehydrogenase, and deranged liver functions. His other inflammatory markers were high as well, suggesting a multisystem inflammatory syndrome: COVID- 19 related MIS-C, His nasal swab RT-PCR for SARS-CoV-2 was negative and there was no history of contact with and COVID-19 patient. Later on day 7 of admission, his antibody titers against SARS-nCoV-2 were positive. His Ultrasound abdomen did not reveal any abnormality and echocardiography showed normal coronaries with global hypokinesia. Differential diagnoses considered were; septic shock, rhabdomyolysis causing renal failure, and rapidly progressive glomerulonephritis. He was started on IV methylprednisolone (30mg/kg) considering MIS-C as the first diagnosis, along with broad-spectrum antibiotics. He started having stable blood pressures from the second day onwards and gradual tapering of inotropic support started. Total 6 doses of IV methylprednisolone were given over 6 days and he was weaned off from inotropes and mechanical ventilation by day 10 of admission. Even after having stable blood pressures and no requirement of respiratory support he remained oliguric with a urine output of less than 0.1ml/kg/hour. So because of persistent acute kidney (AKI), nephrotic range proteinuria with Red Blood Cells (RBCs) in urine at presentation, the decision to do kidney biopsy was taken.

Table I: Investigations at the time of admission

Investigations	Done at admission	Reference range
Hemoglobin (gm/dL)	12.1	10.5-13.5
Total leukocyte counts (cells/mm^3)	30460	4500-13500
Platelet Counts (10^{3}cells/mm^3)	170	150-400
C- Reactive Protein (mg/L)	240	<10
Serum Ferritin (ng/ml)	1868	14-124
Lactate Dehydrogenase (U/L)	840	120-246
Serum triglycerides (mg/dL)	234	<150
Random Blood sugar (mg/dL)	154	70-160
SGOT (U/L)	85	15-40
SGPT (U/L)	54	10-55
Serum Albumin (gm/dL)	2.6	3.7-5.6
Total Serum Bilirubin (mg/dL)	1.8	<1.3
Direct serum Bilirubin (mg/dL)	0.8	<0.3
Serum Lipase (U/L)	429	23-300
Serum Amylase (U/L)	57	30-110
Blood Urea (mg/dL)	176.3	11-38
Serum Creatinine (mg/dL)	3.00	0.6-1.0
Serum Sodium (mmol/L)	132	137-145
Serum Potassium (mmol/L)	4.1	3.7-5.4
Serum Uric Acid (mg/dL)	10	2.7-6.7
Serum Calcium (mg/dL)	8.7	8.8-10.1
Serum Phosphorus (mg/dL)	4.9	3.3-5.4
Serum Chloride (mmol/L)	93	102-112
Serum alkaline phosphatase (U/L)	140	178-455
Serum Cholesterol (mg/dL)	106	<170
iPTH (CLIA-pg/ml)	490	14-72
25(OH) Vitamin D (ng/ml)	3.000	30-76
Urinary Protein (Dipstick)	4+	
Urine RBCs	15-20/HPF	
Dysmorphic urine RBCs	<10%	
Urinary casts	Nil	
Urinary Sugar	1+	
Urine Ketones	Nil	
Blood Culture	Sterile	
Urine Culture	Sterile	

Peritoneal Fluid Microscopy	No micro-organism seen Occasional polymorph seen	
Peritoneal Fluid culture	Sterile	
Complement C3 (immunoturbidometry –mg/dL)	57.90	80-120
Antinuclear Antibody (EIA) units	6.39	<20.0
Anti ds DNA (EIA- IU/ml)	10.93	<30.00
Serum D-Dimer (mg/L FEU)	18.7	<0.50
Serum Fibrinogen (mg/dL)	117	200-400
Serum Creatine kinase (U/L)	>20000	<171.0
Serum CPK-MB (ng/ml)	125.6	<6.22
Serum Troponin I (pg/ml)	2160	<26.20
Prothrombin Time (Sec)	10.6	14
Activated Partial Thromboplastin Time(Sec)	46.8	33
Ultrasound abdomen	Normal	
Chest X-Ray	Normal	
Echocardiography	Global Hypokinesia and normal coronaries	
SARS nCoV 2019 RT-PCR	Negative	
Anti SARS CoV 2 Antibodies Total (COI)Day 7	24.880	0.000-1.000

Ultrasound-guided kidney biopsy was done on day 14 of admission at serum creatinine of 3.5mg/dl. Renal biopsy (Figure-1) revealed non-proliferative morphology of the 27 glomeruli seen, none was globally sclerosed. Tubules show focally prominent cytoplasmic vacuolar change and diffuse severe acute injury. Several granular casts sloughed epithelial & few pigmented coarse casts are seen in tubular lumina. Patchy interstitial edema & focal mild chronic interstitial inflammation are noted. Perl's stain shows few hemosiderin/iron-containing histiocytes in peritubular capillary lumina & interstitium. Blood vessels in biopsy slides were unremarkable for any evidence of thrombotic microangiopathy and vasculitis. The immunofluorescence study was negative for IgG, IgM, IgA, C3, C1q, Kappa, and lambda stains. Ultrastructural examination showed foot effacement of 10% of glomeruli, glomerular basement membrane thickness was normal and no tubuloreticular inclusion or viral particles were seen.

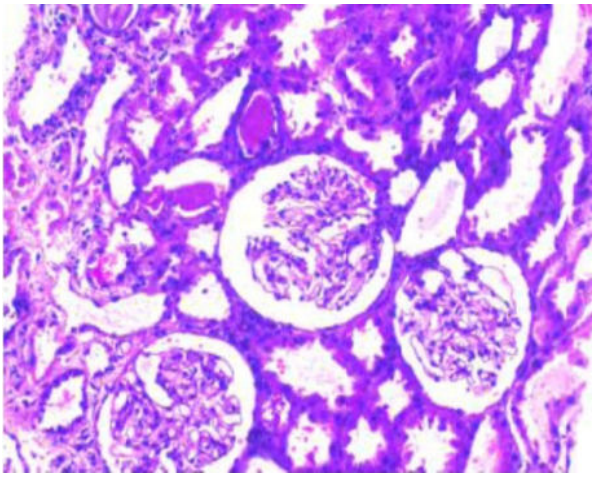

Figure 1: Kidney biopsy

The child continued on intermittent hemodialysis and 2mg/kg steroids (60mg/ day prednisolone). Eventually, after 20 days he started having an increase in urine output and is currently off dialysis with Serum creatinine of 0.39mg/dl and urine examination showed trace proteinuria on dipstick with no RBCs in urine.

DISCUSSION:

Multisystem inflammatory syndrome in children (MIS-C) is defined by CDC[1] as An individual aged <21 years presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization with multisystem (>2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological); AND No alternative plausible diagnoses; AND Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks before the onset of symptoms.

There have been various descriptive case series on the presentation of MIS-C in children in different countries[5-10]. According to Jameela et.al[11] study, patients with AKI had significantly more pediatric intensive care admissions (PICU) (32% vs. 2.8%, p< 0.001) and mortality (42% vs. 0%, p< 0.001). Most children in the above series presented with either fever along with features resembling Kawasaki disease or toxic shock syndrome7. Risk factors for the development of AKI incases of MIS-C include older age, requirement of mechanical entillion, and vasopressor need along with high inflammatory markers (C - reactive protein and Serum Ferritin) and lymphopenia[12].

Our patient presented primarily with a short duration of fever with acute abdomen and dark color urine along with oliguria. To date, there is very limited information available[11,13,14] about the urinary findings in acute kidney injury caused by COVID-19. Our patient had active urinary sediment (nephrotic range proteinuria-dipstick 4+ with RBCs and WBCs) dysmorphic RBCs was less than 10% on urine microscopy. Rhabdomyolysis-associated kidney injury was thought as the cause of AKI but myoglobinuria could not be tested due to anuria. Rhabdomyolysis due to COVID -19 has been described earlier[15] but that patient did not have renal failure. A similar presentation can also be seen in complicated malaria and enteric fever, both of which are endemic in our part of the country so they were excluded by malaria antigen testing and sterile blood culture report. Because of rapidly progressive renal failure, low complement levels, and active urinary sediment working diagnosis of Rapidly Progressive Glomerulonephritis was kept in differential diagnosis list after the first set of investigations and RT PCR negative for SARS-CoV-2. Pathogenesis of AKI in MIS-C is complex and poorly understood as of now and it is hypothesized that AKI occurs due to viral immune responses, cytokine storm, hypoxemia, circulatory collapse, reduced oral intake prothrombotic effects, and direct injury through ACE2 receptor interaction. After our case and a previous case of rhabdomyolysis in a child[15], rhabdomyolysis seems to be an important presentation of COVID-19 in children. Retrospectively all can be explained by MIS-C except the 4+ proteinuria on dipstick which we speculate was due to highly concentrated urine or severe tubular damage. The child has not returned to follow-up after the discharge so repeat C3 was not done. Proteinuria of any degree is associated with poor prognosis and increase in hospital mortality [16].

Though there has been a good review published by Deep A. et. al[17] for the renal replacement therapy in children with COVID19, there are no guidelines to treat AKI in MIS-C as of now, many drugs apart from steroids have been tried including Remdesivir, Tocilizumab, Azithromycin, Intravenous Immunoglobulin (IVIg). We treated our patients with high-dose intravenous methylprednisolone; Intravenous immunoglobulin is not given due to normal echocardiography. The patient recovered completely and was discharged in stable condition on tapering doses of steroids.

In conclusion, we may state that COVID-19 induce MIS-C can present as a rapidly progressive renal failure with rhabdomyolysis and can successfully be treated with high dose steroids only, in absence of coronary artery abnormalities on echocardiography with a satisfactory outcome.

(E) **Keywords:** Rhabdomyolysis, Acute Kidney Injury, COVID-19
(F) MIS-C due to COVID-19 with Rhabdomyolysis and AKI
(G) Characteristics of Pediatric AKI in COVID-19

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