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Case Report

Features of COVID-19 post-infectious cytokine release syndrome in children presenting to the emergency department

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ABSTRACT

The 2019 coronavirus disease (COVID-19) has not appeared to affect children as severely as adults. However, approximately 1 month after the COVID-19 peak in New York City in April 2020, cases of children with prolonged fevers abruptly developing inflammatory shock-like states have been reported in Western Europe and the United States.

This case series describes four previously healthy children with COVID-19 infection confirmed by serologic antibody testing, but negative by nasopharyngeal RT-PCR swab, presenting to the Pediatric Emergency Department (PED) with prolonged fever (5 or more days) and abrupt onset of hemodynamic instability with elevated serologic inflammatory markers and cytokine levels (IL-6, IL-8 and TNF- α).

Emergency physicians must maintain a high clinical suspicion for this COVID-19 associated post-infectious cytokine release syndrome, with features that overlap with Kawasaki Disease (KD) and Toxic Shock Syndrome (TSS) in children with recent or current COVID-19 infection, as patients can decompensate quickly.

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1. Introduction

The 2019 coronavirus disease (COVID-19) caused by SARS-CoV-2 was declared a global pandemic by the World Health Organization (WHO) on March 11, 2020. Although children of all ages are susceptible to COVID-19, clinical manifestations have generally been reported as less severe than in adults [1]. As of May 2 2020, the U.S. CDC reported 17,982 confirmed cases of COVID-19 in American children <18 years old with at least 3 deaths in children <15 years old.

It is speculated that children have had milder illness for several reasons. First, ACE2, which is the likely cell receptor of SARS-CoV-2, may be less developed leading to decreased ability of the virus to bind in children [2]. Additionally, children may have cross-immunity from other viral infections, and/or their developing immune systems may respond to SARS-CoV-2 differently [1].

On April 26, 2020, the Pediatric Intensive Care Society in the United Kingdom issued an alert that children of all ages are presenting with a

multi-system inflammatory state requiring intensive care across their region. They describe children with overlapping features of Toxic Shock Syndrome (TSS) and atypical Kawasaki Disease (KD) with blood parameters consistent with severe COVID-19 in children. They have observed this in children with confirmed RT-PCR positive SARS-CoV-2 infection as well as children who are RT-PCR negative.

Below, we describe four similar COVID-19 serology positive, RT-PCR negative patients who presented to our New York City Pediatric Emergency Department (PED) approximately 1 month from the peak of 6207 new COVID-19 cases reported on April 6, 2020. All four patients developed a similar multi-system, inflammatory state requiring admission to the Pediatric Intensive Care Unit (PICU).

2. Case reports

2.1. Case 1

A 13-year-old male with hypothyroidism was brought to the ED by his father for 1 day of rash, and 6 days of fever, cough, fatigue and myalgias. On the sixth day of illness, he developed bilateral conjunctivitis, a truncal rash, and redness of his palms. He had a few days of abdominal discomfort and loose stools with several isolated episodes of nonbloody, nonbilious emesis over this time period. He also endorsed a mild intermittent frontal headache. The patient denied shortness of breath or sore throat. His father had suspected COVID-19 infection one month prior, with the patient being asymptomatic at the time of the father's illness.

Abbreviations: COVID-19, 2019 coronavirus disease; KD, Kawasaki Disease; TSS, Toxic Shock Syndrome; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2.

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There was no history of recent travel or contact with any COVID-19 positive individuals.

The patient's triage vital signs were T 38.2 °C, HR 119, RR 20, BP 96/50, SPO2 98% RA. Examination was notable for a well appearing boy with bilateral limbic sparing conjunctivitis without discharge, an erythematous tongue and erythematous posterior oropharynx, a maculopapular rash on his chest and erythema of his bilateral hands. There was no lymphadenopathy, and he was breathing comfortably with clear lungs. Abdomen was soft and non-tender.

Laboratory data are presented in Table 1 and chest x-ray (CXR) imaging in Fig. 1.

While in the PED, he developed hypotension and was resuscitated with 60 mL/kg of isotonic fluid. He was admitted to the PICU for pressor support. Broad spectrum antibiotic coverage was initiated with meropenem and linezolid. Repeat CXR several hours later showed new hazy opacities in both lower lungs concerning for atypical viral pneumonia. Over the next 12 h, the patient had worsening hypoxemia requiring escalation in care to BiPAP, which rapidly progressed to respiratory failure requiring intubation. An echocardiogram showed coronary artery dilatation and moderately depressed left ventricular systolic function (Ejection Fraction = 47%). He was treated with enoxaparin in the setting of markedly increased D-dimers. Two repeated SARS-CoV-2 PCRs (including an endotracheal sample) were negative, but the COVID-19 IgG antibody test was positive. The patient continued treatment with broad spectrum antibiotics and was treated with IVIG, tocilizumab and anakinra for presumed COVID-19 cytokine storm with elements of atypical KD disease and elements of TSS. Repeat labs were significant for elevated troponin (3.42 ng/mL), rising BNP (1411.10 pg/mL), D-dimer (7.29 UG/mL) and inflammatory markers.

Table 1
Laboratory data.

	Case 1	Case 2	Case 3	Case 4
White cell count (x10E3/uL)	10.9	17	5.1	5.6
Absolute lymphocyte count (cells/m3)	436	340	245	610
Hemoglobin (G/DL)	13.1	11.2	11.6	11.0
Platelets (x10E3/uL)	205	111	140	123
PT (seconds)	14.4	16.5	16	15.1
INR	1.2	1.4	1.3	1.2
C-reactive protein (mg/L)	363.8	284.6	202.2	249.9
Erythrocyte sedimentation rate (mm/h)	66	63	46	92
Procalcitonin (ng/mL)	25.49	11.39	2.35	16.74
LDH (U/L)	472	287	408	288
BNP (pg/mL)	120.6	3068.52	72.44	132.7
D-dimer (UG/mL)	3.26	2.23	4.46	3.75
Ferritin (NG/mL)	2010	1197	850	288
Fibrinogen (mg/dL)	948	782	531	614
Troponin (ng/mL)	0.02	0.32	0.05	<0.01
Lactate (MMOL/L)	1.9	1.6	3.2	2.8
AST (U/L)	95	28	67	38
ALT (U/L)	93	24	47	23
Respiratory viral pathogen testing by RT-PCR	Negative	Not performed	Negative	Not performed
SARS COV 2 by RT-PCR	Negative	^a Not performed	Negative	Negative
COVID-19 antibody assay, titer	Positive, 960	Positive, 960	Positive	Positive, 960
INTERLEUKIN 6 (normal = 0–5 pg/mL)	286.0	374.0	504	214
INTERLEUKIN 8 (normal = 0–5 pg/mL)	37.8	54.5	149	54.4
TUMOR NECROSIS FACTOR ALPHA (normal = 0–22 pg/mL)	56.5	68.8	49.3	44.4
INTERLEUKIN 1 BETA (normal = 0–5 pg/mL)	0.4	0.6	1.6	0.9
Blood culture	NGTD	NGTD	NGTD	NGTD

Bold signifies abnormal values.

^a Deferred due to positive test 17 days prior.

2.2. Case 2

A 10-year-old male with asthma and recent COVID-19 positive test 17 days prior presented with 5 days of fever, fatigue, poor oral intake, diarrhea, cough and a rash. He described a diffuse erythematous, non-pruritic rash throughout his body. Four days prior to presentation, he was diagnosed with presumptive *Streptococcal* pharyngitis and started on treatment with Amoxicillin. The antibiotic was discontinued once the throat culture was negative. On the day of presentation, he was evaluated by a dermatologist via telemedicine who recommended supportive care for his rash.

Both his parents also had COVID-19. There was no recent travel. The patient did not take any daily medications and was current with his routine vaccinations.

The patient's triage vital signs were: T 35.8, HR 104, RR 28, BP 70/35, SpO2 96% RA. On physical exam, he was in no acute distress but complained of generalized discomfort. He had a diffuse erythematous, blanching, maculopapular rash on the neck, chest, abdomen, back and extremities (including the palms and soles) with dusky areas on the back. He had mild, bilateral non-purulent conjunctival injection without oral lesions. He was tachycardic with normal rhythm and good air entry bilaterally in the lungs with normal respiratory effort. His abdomen was soft, nondistended and nontender. His extremities were warm and well perfused with a brisk capillary refill.

Laboratory data are presented in Table 1. CXR imaging results are presented in Fig. 1.

The patient was resuscitated with 80 mL/kg of normal saline via pressure bag without hemodynamic improvement. He received cefepime and clindamycin to cover for TSS. Vancomycin was held due to concern for acute renal injury as evidenced by azotemia on his labs. The patient was admitted to the PICU for close monitoring and initiation of dopamine peripherally for pressor support in the setting of persistent hypotension. Cardiology performed an echocardiogram, which showed mild regurgitation in both the tricuspid and mitral valves and normal coronary arteries with the exception of slight ectasia of the left anterior descending artery.

In the PICU, the patient was treated with IVIG for atypical KD disease, tocilizumab for the cytokine storm and linezolid was added to cefepime for better inhibition of toxins produced in TSS.

2.3. Case 3

A 5-year-old healthy male presented with 5 days of fever and 1 day of abdominal pain and vomiting. He had a decreased appetite for the past few days but did not have cough, congestion, rhinorrhea, shortness of breath, diarrhea or rash. The family had no sick contacts, and the patient did not have any exposure to COVID-19 positive individuals.

On arrival, the patient was tired-appearing but alert. His initial vital signs showed a temperature of 40.2 °C, HR 156, BP 94/64, RR 31, SPO2 98% RA. Examination was notable for bilateral limbic sparing conjunctivitis without discharge, dry/cracked lips, scattered petechiae on the eyelids bilaterally, and shotty cervical lymphadenopathy. His posterior oropharynx was mildly erythematous. He had tachycardia without a murmur or gallop, clear lungs without retractions or crackles, a soft, non-tender abdomen, and a normal GU exam with no scrotal swelling or testicular tenderness. No rashes were noted.

Laboratory data are presented in Table 1.

During his course in the PED, the patient remained febrile and tachycardic. He was given one 20 mL/kg NS bolus and started on maintenance IVF with D5 NS. A cardiopulmonary POCUS showed scattered B-lines with no lung consolidations, a small pericardial effusion and prominent left main coronary artery, and no thrombus in the IVC, femoral, or popliteal veins. He was given ceftriaxone and clindamycin for coverage of potential TSS. He was admitted to the floor for further management.

The patient remained stable on the floor for about 24 h. During that time he was started on enoxaparin, and had a testicular US showing

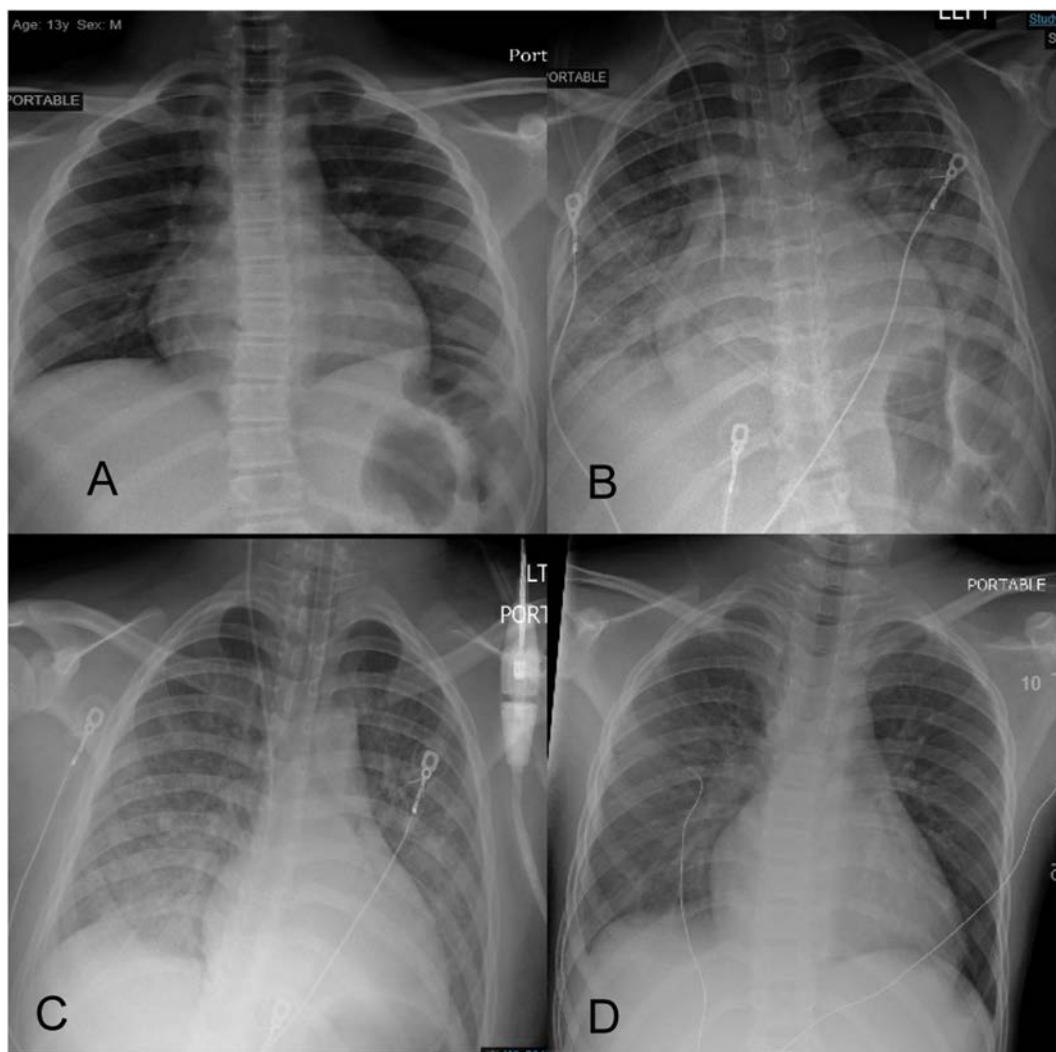


Fig. 1. Patient 1's progression of consecutive portable chest radiographs interpreted by radiologists. A. In ED, "No acute pulmonary disease." B. 17 h later, "New hazy opacities in both lower lungs concerning for atypical viral pneumonia." C. Hospital Day 2, "Hazy bilateral opacities predominantly in the mid to lower lungs concerning for atypical viral pneumonia." Patient 2's portable chest radiograph interpreted by radiologists. D. "Peribronchial thickening with ill-defined airspace opacities in the right mid to lower lung, concerning for atypical viral pneumonia."

bilateral epididymoorchitis and an abdominal US which was remarkable for mild free fluid and borderline gallbladder wall thickening. A formal echocardiogram showed a mildly dilated proximal left anterior descending coronary artery.

A rapid response was called the evening after admission for BP of 61/37. Patient was fluid resuscitated and BP stabilized. However, the following day the patient again had hypotension and was transferred to the PICU and started on dopamine. He was given IVIG and tocilizumab, and continued on ceftriaxone and clindamycin.

2.4. Case 4

A 12-year-old healthy female was referred to the PED for evaluation of appendicitis. She was evaluated the day before at another ED for 1 week of fever, abdominal pain, vomiting and diarrhea. The CT scan of the abdomen showed minimal distention of the appendix with mild prominence of the appendiceal wall, concerning for possible early appendicitis. The entire colon was noted to be filled with fluid and there was mild, diffuse wall thickening, suggestive of mild colitis. Her CXR was normal. The urinalysis had trace ketones and protein without nitrites or leukocyte esterase.

The patient's triage vital signs in our PED were: T 36.7, HR 121, RR 20, BP 101/62, SpO₂ 99% RA. She was tachycardic with a normal rhythm

and good air entry bilaterally without increased respiratory effort. Her oropharynx and palate were erythematous without exudate. Her abdomen was soft, nondistended with some tenderness to palpation in the epigastrium and both lower quadrants without any peritoneal signs. Her skin was warm and well perfused, without any rashes and a brisk capillary refill. Pediatric surgery evaluated the patient and determined she was not a surgical candidate at this time.

Laboratory data are presented in [Table 1](#).

Due to her persistent tachycardia, she was given a 20 mL/kg fluid bolus and an EKG was obtained which demonstrated sinus tachycardia. Upon reassessment after fluid administration, her vitals were T 39.3, HR 146, BP 81/48. She received 2 more 20 mL/kg boluses of normal saline before transfer to the PICU due to persistent hypotension. Broad spectrum antibiotics coverage with cefepime, vancomycin and metronidazole was initiated.

3. Discussion

Severe COVID-19 symptoms in healthy children have been uncommon. This case series describes four healthy pediatric patients with positive COVID-19 serology who presented with clinical features of atypical KD disease and TSS with laboratory evidence of inflammation and

cytokine storm, requiring admission to the PICU for respiratory support and/or hemodynamic instability.

Common laboratory findings among hospitalized patients with RT-PCR positive SARS-CoV-2 infection include lymphopenia, elevated lactate dehydrogenase levels, elevated inflammatory markers (ferritin, C-reactive protein, and erythrocyte sedimentation rate), elevated procalcitonin and elevated D-dimer. The same laboratory findings were seen in these four children with COVID-19 post-infectious cytokine release syndrome.

Additionally, all four children had an exaggerated cytokine storm with a profoundly elevated IL-6 and elevated IL-8 and TNF- α . Elevations in these cytokines can lead to increased vascular hyperpermeability, multiorgan failure and eventually fatality if the cytokine concentrations remain unabated over time [3,4]. The mechanism of injury during cytokine storm is poorly understood, but an exaggerated initial response that persists over time is associated with poor outcomes [4]. Treatment with tocilizumab was initiated in all four patients to directly inhibit the IL-6 cytokine storm.

Interestingly, three of these four patients presumably had asymptomatic COVID-19 infections, as they reported no recent symptoms of illness yet had positive antibody testing. It is possible that the mechanism of COVID-19 post-infectious cytokine release syndrome in children is a post-infectious phenomenon related to an antibody complex mediated reaction.

Emergency physicians must maintain a high clinical suspicion for post-infectious cytokine release syndrome in children with recent or suspected COVID-19 infection. We recommend a low threshold for laboratory testing, including cytokine markers, and admission for all children with laboratory evidence of a significant inflammatory response. In our experience, they may appear well initially but have a high

propensity for acutely decompensating requiring rapid fluid resuscitation, pressor support, and even intubation.

4. Conclusion

Patients presenting with COVID-19 associated post-infectious cytokine release syndrome appear to present with prolonged fever (5 days or greater) and GI symptoms with or without rash. This syndrome may overlap with features of KD and TSS. However, these patients may decompensate quickly and require resuscitation. Patients who present with this clinical picture should have frequent vital signs and will require admission due to potential for rapid deterioration.

Declaration of competing interest

Temima Waltuch, Prakriti Gill, Lauren E. Zinns, Rachel Whitney, Julia Tokarski, James W Tsung and Jennifer E Sanders have no conflicts of interest.

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