Prolonged Fever: Kawasaki Disease in a Pediatric Patient With COVID-19

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Kawasaki disease (KD) is the leading cause of acquired heart disease. The cardiac clinical features seen with KD require diagnosis and treatment within 10 days of symptoms to decrease the risk of complications. This case report examines the complexity of prolonged fever in a pediatric patient with a positive test for severe acute respiratory coronavirus 2 and meets the KD criteria. J Pediatr Health Care. (2022) *XX*, 1−5

KEY WORDS

COVID-19, Kawasaki disease, cardiac findings, prolonged fever, fever

INTRODUCTION

Fever is a common symptom seen in illnesses affecting children and adolescents. In general, fever is one of the body's main immune response reactions to infection, suggesting that fever can be beneficial and self-limiting. Often parents will seek medical attention when their child develops a fever. Fever in children accounts for up to 30% of primary care and emergency department visits (Urbane et al., 2019).

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COVID-19 is a viral infection, and similar to most viral infections, fever is a frequent symptom. In 2022, approximately 6.8 million children tested positive for COVID-19, thus increasing the reported total of children who have tested COVID-19 positive in the United States since the beginning of the pandemic to nearly 14.7 million (American Academy of Pediatrics, 2022). Children aged < 18 years represent 18.5% of the total number of COVID-19 cases and comprise 22.2% of the U.S. total population (Center for Disease Control and Prevention [CDC] 2022a). Although mortality from COVID-19 is rare in the pediatric population, 1,462 children aged ≤ 18 years have died of the virus (CDC, 2022b).

The incubation period for COVID-19 ranges from 2 to 14 days, with an average of 6 days (CDC, 2020). Potential signs and symptoms of COVID-19 in children include fever, cough, nasal congestion, headache, sore throat, fatigue, myalgia, shortness of breath, difficulty breathing, decreased appetite, abdominal pain, diarrhea, nausea, and vomiting (CDC, 2020). The most common symptoms in children with COVID-19 are cough and fever (CDC, 2020). However, some children who test positive for COVID-19 may be asymptomatic.

Although children with COVID-19 are at lower risk of severe illness compared with adults, children can still develop severe illness and complications from the virus (CDC, 2020). In addition, children aged < 1 year and those with underlying medical conditions, including obesity, diabetes, asthma, and cystic fibrosis, are at increased risk of more severe illness from COVID-19 (CDC, 2020). The signs and symptoms of COVID-19 can mimic other illnesses such as influenza, rhinovirus, seasonal allergies, pneumonia, mononucleosis, and streptococcal pharyngitis, making accurate diagnosing challenging. Though children infected with COVID-19 are less likely to require hospitalization, approximately one in three children hospitalized with COVID-19 need intensive care treatment, similar to the rate seen in adults (CDC, 2020; Kim et al., 2020). This case report examines the complexity of

prolonged fever in a pediatric patient with a positive test for severe acute respiratory coronavirus 2 (SARS-CoV-2) and meets the Kawasaki disease (KD) criteria.

CASE PRESENTATION

A 30-month-old girl presented to the primary care clinic accompanied by her parents and 5-year-old sister. The patient had a history of fever for 4 days, with 39.4 °C reported at home that morning. The patient's sibling presented with mild rhinorrhea and tested positive for Sars-CoV-2 at the clinic visit.

Her temperature in the clinic at the time of her visit was 38.1 °C, and her other vital signs were age appropriate. The patient was awake and alert with slight irritability. Her physical examination showed mild clear rhinorrhea. Her oral mucosa was pink and moist. Her sclerae were white with no eye discharge. The tongue was a normal appearance. The tympanic membranes were normal appearing. She had no adenopathy. She had no signs of respiratory distress. Her breath sounds were clear to auscultation with no stridor, retractions, or nasal flaring. Her abdomen was soft and nontender, with audible bowel sounds. The skin was warm, dry, and intact, without rashes or lesions.

Despite her sibling testing positive, the patient tested negative for Sars-CoV-2 on rapid COVID testing, and negative on rapid influenza and rapid strep testing. A strep culture was sent, which resulted in a negative result. The patient was sent home with guidance for fever management and to return to the clinic if the fever did not resolve in 24 hr.

The fever continued, and the patient returned to the clinic for reexamination on day 6 of the fever. On representation to the clinic, her temperature was down to 37.6 °C. The child's mother reported that the patient developed dry, cracked lips on day 5 of fever. In addition, she had injected sclerae bilaterally without discharge. A macular diffuse blotchy nonpruritic rash was observed scattered across her body, including her face, that had started on day 5. In the clinic, she tested positive for Sars-CoV-2 and negative for influenza A and B on rapid testing.

PHYSICAL EXAMINATION

Her vital signs included a temperature of 37.6 °C, a pulse of 106 beats per min, and a respiratory rate of 24 breaths per min. On physical examination, the patient had dry, cracked lips. Her sclerae were injected bilaterally with no discharge. The tympanic membranes were normal in appearance, with normal landmarks and cone of light. She had no adenopathy. She had mild rhinorrhea. Her lungs were clear to auscultation with no signs of respiratory distress. Her heart sounds were clear, with no murmur. Her abdomen was soft and nontender. She had mild swelling in both hands. She had a macular blotchy rash on her body and face. She was awake and alert, with noted increased irritability from her previous examination.

HOSPITAL COURSE

The provider consulted an infectious disease expert with parental permission and shared pictures of the rash and cracked lips through the electronic medical record system. It was determined that although the patient was positive for Sars-CoV-2, she also met the diagnostic criteria for KD. The patient was admitted to the local Children's Hospital for further evaluation and care.

On admission, inflammatory markers were elevated with an erythrocyte sedimentation rate (ESR) of 94 mm/hr (0−20 mm/hr) and C-reactive protein (CRP) 5.8 mg/100 ml (0−0.8 mg/100 mL). The patient was positive on polymerase chain reaction (PCR) for Sars-CoV-2 and rhinovirus/enterovirus. An echocardiogram (ECHO) showed normal coronary artery origins and proximal courses, normal-size right and left ventricles, and normal cardiac valve morphology and function, with no evidence of pulmonary hypertension or pericardial effusion. The patient developed additional swelling of her hands and feet on day two of hospital admission. The infectious disease consultant confirmed the diagnosis of KD. On day 2 of hospitalization, intravenous immunoglobulin (IVIG) was administered, and the patient was started on low-dose aspirin 0.5 tablets (40.5 mg) orally once a day (Sakulchit et al., 2017).

The patient was afebrile on day 3 of hospitalization. Her CRP was 4.8 mg/100 mL on day 3 and 3.9 mg/100 mL on day 4 of the hospital course. Her rash faded, and she started peeling between interweb spaces of her hands. Her lips became less red and cracked over the 4-day hospital stay. The patient was discharged on day 4 on low-dose aspirin for 6 weeks and scheduled for follow-up with the infectious disease team; repeat ECHO and CRP were scheduled for 1 week postdischarge.

The patient was seen for follow up at the primary care clinic 2 days after hospital discharge. At this time, the patient remained afebrile. Her parents reported continued improvement in her cracked lips, and her physical examination was otherwise unremarkable.

Six days after hospital discharge, the patient represented with a fever of 38.5 °C. Her mother reported she had flushed cheeks and edematous fingers. Her mother contacted the infectious disease provider, and she was readmitted. The patient's physical examination revealed mild nasal congestion and cracked lips; there was no cough, eye redness or discharge, or rash other than flushed cheeks and peeling skin near her fingernails. Her CRP had increased to 4.5 mg/100 mL (3.9 mg/100 mL at discharge), and the patient had new anemia and thrombocytosis. Her serum iron was 18 μg/dL (45−143 μg/dL), total iron binding capacity 258 μg/dL (280−400 μg/dL), 7% saturation (7% to 53%), and transferrin 184 mg/100 mL (152−345 mg/100 mL). Her COVID PCR was negative for Sars-CoV-2. The patient was given a second dose of IVIG. A repeat ECHO revealed the left anterior descending artery (LAD) was mildly dilated with a z-score of 3.0 and demonstrated luminal irregularity. The z-score is a classification system that uses the standard deviation of a value to compare to the normal distribution

and is used to measure coronary artery involvement. A z-score < 2.0 standard deviation is considered normal, whereas a z-score between 2.5 to < 5.0 is considered a small aneurysm of the coronary arteries (Hörl et al., 2021). Because of a LAD z-score of 3.0, the patient met the high-risk criteria for KD. She clinically improved after an overnight dose of IVIG and appeared less fatigued. She still had edematous digits and peeling palms.

MANAGEMENT

Because of her cardiac changes, high-risk KD protocol and intravenous steroids were started, methylprednisolone, 2 mg kg^{-1} daily for 5 days, followed by an oral steroid taper (Sakulchit et al., 2017). On day 3 of hospitalization, CRP had decreased to 2.2 mg/100 mL (reference range and units 0–0.8 mg/100 mL), and by day 4, CRP had decreased further to 1.0 mg/100 mL. A repeat ECHO was done on day 4 of hospitalization, showing the LAD was no longer dilated. She was discharged on day 5 of hospitalization with CRP 0.6 mg/100 mL. Discharge medications included aspirin, 40.5 mg (half a tablet) by mouth daily, and famotidine, 8 mg/mL suspension 0.6 ml (0.5 mg/kg/dose) twice a day while on steroid taper (Sakulchit et al., 2017). Repeat CRP 6 days postdischarge remained normal at < 0.3 mg/100 mL, and repeat ECHO was normal. The patient was weaned off steroids, and her aspirin was discontinued 4 weeks following the second hospitalization. Her follow-up plan included annual visits with the infectious disease team per high-risk KD protocol and for routine primary care. Because of receiving IVIG, any administration of live vaccines was deferred for 11 months (American Academy of Pediatrics, 2018). The patient received her first COVID vaccine, and quadrivalent inactivated influenza vaccine at the primary care clinic 3 months after hospitalization.

DISCUSSION

KD is the leading cause of acquired heart disease and the second most common vasculitis in children (John & Brady, 2020). KD is also known as mucocutaneous lymph node syndrome because of its association with cervical lymph node enlargement and involvement of mucus membranes of the mouth, eyes, and throat (John & Brady, 2020). As this case demonstrates, the main symptom of KD is acute prolonged, persistent fever. Fever is a common symptom with viral infections and, in most cases, tends to resolve in 3–5 days. Other steps are required to determine the underlying cause when the fever is persistent and prolonged. With KD, the fever is typically high, 102°F or higher, which adds to the degree of concern and further contributes to parental anxiety about their child's illness.

The exact etiology of KD remains unknown. It was first identified in Japan in the 1960s and is now seen worldwide. Children aged between 6 months and 5 years are the most susceptible to KD, with the peak incidence seen in children between 6 and 24 months (Sakulchit et al., 2017). Although the exact cause of KD is idiopathic, cases peak in the late winter and early spring months. This case occurred during the late spring/early summer. Japan has the highest incidence of KD cases. It is uncertain whether this is from an increased awareness of the disease in its country of origin or a genetic component. In the United States, children of Asian/Pacific Islander descent have the highest hospitalization rate for KD, which stresses the need for further investigation of this health disparity (John & Brady, 2020). The patient in this case report met this norm.

KD is a diagnosis of exclusion which adds challenge. Consequently, diagnosis is based on a specific criterion and supporting diagnostic testing. The criteria to meet the diagnosis for KD include prolonged fever for 5 days or more and the presentation of at least four out of five additional symptoms, including bilateral conjunctival injection, lips, and oral cavity changes, unilateral cervical lymphadenopathy, rash, and swelling of hands or feet. Laboratory investigations are not diagnostic but useful to help rule out another diagnosis (John & Brady, 2020). Standard diagnostic testing should include complete blood count with differential and platelet count, CRP, ESR, and comprehensive metabolic profile. Typical laboratory findings include elevated inflammatory markers, CRP and ESR, and neutrophilia with bands and elevated platelets (John & Brady, 2020).

The diagnostic laboratory results in this case report support the diagnosis of KD. The patient had elevated inflammatory markers. Both CRP and ESR were elevated on hospital admission. As shown in the Table 1, the CRP values were monitored throughout both hospitalizations and follow-up visits, demonstrating a downward trend as the patient improved. The clinical improvement observed, plus the eventual return of the CRP value to the normal range, further demonstrates the accuracy of the diagnosis of KD in this patient.

TABLE. 1. C-reactive protein (CRP) and days of illness

Hospitalization course	CRP,[a] mg/ 100 mL	Day of illness
Hospitalization day 1 (fever × 6 days)	5.8	6
Hospital day 3 (afebrile)	4.8	8
Hospital day 4 (discharge)	3.9	9
Readmission to hospital day 1 (fever × 2 days)	4.5	15
Day 3 (afebrile)	2.2	17
Day 4	1.0	18
Day 5 (discharge)	0.6	19
Follow-up visit	< 0.3	25

[a]*Reference range, 0–0.8 mg/100 mL.*

Because of the ongoing COVID-19 pandemic, PCR testing has become more prevalent to assist in diagnosing and infection control measures, especially for patients requiring hospitalization. This case report is no exception to this new standard. The patient tested positive on PCR for Sars-CoV-2 and rhinovirus/enterovirus. COVID-19 symptoms mimic other illnesses, and symptoms such as fever, conjunctival injection, and even rash have been reported in children with COVID-19 infection (Danthuluri & Grant, 2020). Other symptoms that can be exhibited with KD and COVID-19 include abdominal pain, diarrhea, irritability, arthralgia, and vomiting. In this case report, the patient showed signs of irritability. This can be difficult to ascertain without caregiver input because children can be fearful of examination and may be extremely irritable while the provider is in proximity. Here, the parents and the provider noted irritability at home and in the clinic.

The similarities in clinical symptoms of KD and COVID-19 are further complicated by the emergence of a multisystem inflammatory syndrome in children (MIS-C). MIS-C is considered a late immune response to Sars-CoV-2 infection. Most children with MIS-C present with abdominal pain, diarrhea, and vomiting and a history of COVID-19 exposure or a positive Sars-CoV-2 PCR test within 4 weeks of the onset of symptoms (Waseem et al., 2022). Similar to KD, MIS-C does not possess definitive diagnostic tests. Elevated inflammatory markers (CRP and ESR) are evident in both KD and MIS-C. In addition, MIS-C platelet counts drop as opposed to KD, which typically shows a rise after day 5 of illness (Waseem et al., 2022). Both KD and MIS-C are associated with coronary artery changes. However, MIS-C patients are more likely (50%) to initially present in shock as opposed to KD patients (5%; Waseem et al., 2022). The patient in this case report did not test positive for Sars-CoV-2 until day 6 of illness; therefore, MIS-C was not a high concern despite elevated inflammatory markers.

The cardiac clinical features seen with KD are the main reason diagnosis and treatment must begin expeditiously within 10 days of symptom onset. Because of this risk, one of the main goals of treatment is to prevent coronary artery aneurysms. In the acute phase, 15% to 25% of untreated children and < 5% of treated children can develop coronary artery aneurysms (de La Harpe et al., 2019). Initiating IVIG therapy and acetylsalicylic acid (ASA) is crucial. ASA has an antiplatelet effect and anti-inflammatory properties. After initiating high-dose ASA, treatment is tapered over a 6−8-week period (John & Brady, 2020). ASA is discontinued if the ECHO is normal. If coronary artery abnormalities develop or do not resolve, ASA or other antiplatelet therapy is used indefinitely (John & Brady, 2020). For this case report, the patient was started on IVIG and ASA within 7 days of symptoms and had mild cardiac changes on ECHO, which fortunately resolved.

The long-term prognosis for children with KD is excellent. The disease tends to be self-limiting, and complications are greatly reduced if therapy is started within 10 days of initial symptoms. Possible complications include congestive heart failure, myocardial infarction, myocarditis, pericarditis, and disease recurrence (de La Harpe et al., 2019).

CONCLUSIONS

Throughout the COVID-19 pandemic, we must remain cognizant of other causes of fever in children. KD was first described by Tomisaku Kawasaki, a Japanese pediatrician, in 1967 and continues to be a leading cause of acquired heart disease and, in rare incidences, can be fatal (Green, 2020). This case report is a reminder of the complexity of fever in children and the importance of careful consideration of all possible causes to arrive at the appropriate diagnosis and treatment.

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