

CASE SERIES

Association between Kawasaki Disease and Covid-19 in Children: A Case Series

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ABSTRACT

The global pandemic of Covid-19 has affected people of all age groups. Where the adults have shown specific signs and symptoms of the disease, the clinical spectrum and manifestations in Pediatric patients have not been clearly defined. An association between Covid-19 and Kawasaki disease was first speculated in United Kingdom in April 2020 when a child who previously tested positive for Covid-19 presented with features of Kawasaki disease. Following this, several other cases emerged linking a Kawasaki-like multisystem inflammatory syndrome in children (MIS-C) with Covid-19. Since the exact pathophysiology is not known, children with MIS-C require aggressive treatment and close follow-up after discharge. The aim of this case series was to highlight this association with the help of four cases each of which showed symptoms of Kawasaki disease along with a history of Covid-19 infection. This will help in increasing awareness of the Pediatricians for early management to prevent morbidity and mortality.

Keywords: Mucocutaneous Lymph Node Syndrome; Pediatric Multisystem Inflammatory Syndrome; MIS-C; SARS-COV-2.

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INTRODUCTION

Children constitute a small proportion of the reported cases of Covid-19¹. However, the evolving knowledge of the disease has called attention to a rare form of vasculitis known as Kawasaki disease in children who have a history of Covid-19 infection. The profuse multi-systemic inflammation that has been described, as a feature of both SARS-COV-2 and Kawasaki-like multisystem inflammatory syndrome gives a hint regarding the pathophysiology of MIS-C². Since much remains unknown regarding the clinical implications of the association between Kawasaki disease and Covid-19 and their possible multisystem involvement, therefore this case series will help summarize the available evidence to provide insight into the clinical spectrum of MIS-C associated with Covid-19 and provide direction for future research studies.

CASE 1

A four and half years old previously healthy and immunized female presented to a local GP after she

developed high-grade fever occurring every 3 hours. She also had an earache and a painful, tender swelling below her left ear. She was prescribed with oral antibiotic (amoxicillin), anti-histamine and paracetamol. After the first dose of amoxicillin, she developed erythematous rash on palms and soles with pinpoint rashes on face, arms and genitals. She was taken to a local hospital where she was started on azithromycin and amoxicillin was discontinued. Since her fever persisted, her blood test for typhoid fever was done and she was sent home. By the time, she presented to us on 4-05-2020. She was having a fever for 6 days, left sided neck swelling, pinpoint rashes, redness of eyes and throat ache for approximately 5 days. Erythematous rash of hands and soles had resolved by this time.

On examination, she had cracked lips, hyperemic throat, strawberry tongue, pinpoint rashes on arms and face, left sided cervical lymphadenopathy and non-purulent conjunctivitis. A provisional diagnosis of Kawasaki Disease was made. Her

laboratory investigations were sent which showed a total leukocyte count of 168000 with increased neutrophil count (74%), platelets were 532,000, raised C.R.P (193.2), E.S.R was 81, ASO titer which was already done (from outside) was less than 200. Cardiac evaluation and echocardiography was done which showed a structurally normal heart with no cardiac involvement. A Covid-19 PCR test was also sent based on patient's history of travel (visiting from Lahore) however; it came out to be negative. Based on the above findings a diagnosis of

Kawasaki disease was made and patient was given intravenous immunoglobulin once along with aspirin. She was observed for 36 hours, she remained afebrile, her rashes and conjunctivitis improved with reduction of the cervical swelling hence, she was discharged on tablet aspirin with an advice to follow up. After a week, patient visited the outpatient department; she had improved but had developed periungual peeling of fingers (Figure 1). She was advised to continue aspirin for 6 weeks.



Figure 1: Periungual desquamation of fingers.

CASE 2

A 10-year old previously healthy male weighing 27kg, resident of Larkana, presented with the complaints of fever, vomiting and generalized weakness since 10-12 days, decreased appetite for 3-4 days and redness of the eyes (bilateral) along with rashes all over the body for 2 days. Before presentation, the child had received a 3 days course each of oral amoxicillin and oral azithromycin, prescribed at a local clinic in Larkana. By the time the patient presented to us on 28-06-2021, he was vitally stable but appeared lethargic, with a mildly hyperemic and coated tongue, conjunctival redness, right cervical lymphadenopathy (2cm), and maculopapular rash all over the abdomen and palmer erythema. His baseline laboratory investigations were done which showed an elevated neutrophil count (91%), a

raised CRP of 143 U/L. MPICT was negative, and LFTs were within normal range. Covid PCR was done which came out to be negative however, Covid serology showed a positive IgG. Patient experienced no respiratory complaints and maintained oxygen saturation at room air. Under the suspicion of Atypical Kawasaki Disease, the patient was given one dose of intravenous immunoglobulin and was started on aspirin. While ECG showed normal findings, echocardiography showed small aneurysmal dilation of left distal coronary artery (4 mm in diameter). The patient showed improvement and remained afebrile for more than 24 hours following the IVIG dose. He was discharged with an advice to continue aspirin and follow-up in OPD for a repeat echocardiography (Figure 2).



Figure 2: Echocardiograph showing aneurysmal dilation of left distal coronary artery.

CASE 3

2 years old, male weighing 10.2kg presented as a recovered case of Kawasaki Disease and Covid-19. He was admitted at another tertiary care hospital in the first week of June 2020 where he tested positive for Covid-19 and was treated with intravenous immunoglobulin. Covid PCR became negative on 23 June 2020. He presented on 18-07-2020 (approximately 6 weeks after the first episode) with the complaints of fever and rash on the body for 2 days. There was no cough or breathing difficulty. At presentation patient was vitally stable with rashes all over the body. His lab investigations were sent which showed an increased total leukocyte count (lymphocyte predominance) and a raised CRP (86.5) and ESR (85). His LFTs, ferritin, procalcitonin, troponin-1 and D-dimers were also done which were normal. He was started on IV antibiotics (I/V ceftriaxone) along with continuation of oral aspirin (maintenance dose).

A Chest X-ray and cardiac echocardiogram was also performed (Figure 3). Where the former was normal, the latter showed perivascular brightness (findings similar to the Echo done before in June 2020). Patient experienced 2 fever spikes on the 1st day of admission following which he remained afebrile however skin rash continued to appear on/off along with a rising trend of CRP (repeat CRP: 128.9). Based on all the findings a relapse of Kawasaki Disease was suspected and patient was given IVIG (second dose: 2g/kg stat). Antistreptolysin O titer (ASOT), antinuclear antibody (ANA) profile and serum albumin were within normal range. Patient's rash eventually resolved and he was discharged on aspirin for 6 weeks and was called for follow up.



Figure 3: Echocardiograph showing perivascular brightness of left coronary artery.

CASE 4

3 years old male child, weighing 16.5 kg, presented with the complaints of fever, abdominal pain, loose stools, and vomiting for 2 days. At the time of the presentation, the patient was irritable with a fever of 102F. There were no remarkable findings on systemic examination. All baseline labs were sent along with a chest X-ray that was normal. Investigations showed a negative Malarial Parasite and Dengue NS-1 and an increased CRP (225mg/L). The patient was managed with antibiotics (IV meropenem and oral azithromycin). On the second day of admission, he developed a rash on the entire body (maculopapular) mainly on the abdomen with erythema of palms and soles, bilateral non-exudative conjunctival redness and oropharyngeal erythema.

Based on all the clinical findings and a raised CRP a diagnosis of Kawasaki Disease was made. The antibiotics were stopped and patient was given I/V immunoglobulin and aspirin (40mg/kg/day, 6 hourly). An opinion was taken from infectious disease specialist who confirmed the diagnosis of Kawasaki and advised to send a throat culture (negative), Urine DR (normal) and a Covid PCR. The Covid PCR of the patient came out to be positive. The patient however did not experience any respiratory symptoms and maintained saturation at room air. Rest of the lab investigations included LDH which was 492U/L (normal 230-460U/L, D-dimer was 4400 ng/ml FEU (normal 55-1550 ng/ml FEU) and Ferritin was 160 (normal). Patient was kept in isolation and treatment was continued with aspirin and temperature monitoring. An echocardiography was done which was normal. A repeat CRP was sent which were 79. The patient's condition gradually improved over time therefore he was discharged on aspirin and oral paracetamol and was advised to maintain isolation.

DISCUSSION

Kawasaki Disease (KD) or mucocutaneous lymph node syndrome is an acute febrile illness of childhood that is characterized pathologically by vasculitis of medium-sized arteries with a predilection for the coronary arteries making it the leading cause of acquired heart disease in the developed countries^{5,6}. It is a disease of early childhood, with children under 5 years of age having highest annual hospitalization rates⁷. The etiology of Kawasaki Disease is not known. Although certain epidemiologic and clinical features support an infectious origin, still there are features that are not consistent with an infective etiology⁹. In addition, considering the higher risk of KD in Asian children genetic cause also seems likely¹⁰.

Since there are no diagnostic tests available⁵, the diagnosis is done based on a clinical criteria which includes the presence of fever for 5 or more days with at least four of the remaining five symptoms

that includes extremity changes, polymorphous exanthem, oropharyngeal erythema, cracking of lips with strawberry tongue, bilateral non-exudative bulbar conjunctival injection, and cervical lymphadenopathy⁸. When it comes to laboratory findings leukocyte count is normally elevated with neutrophil predominance and an increase in platelets, ESR and CRP are also elevated and must be evaluated since; KD is unlikely if the ESR and CRP are normal after 7 days of fever. There may also be sterile pyuria, mild elevations of the hepatic transaminases, hyperbilirubinemia, and cerebrospinal fluid pleocytosis^{5,11}. Echocardiography and measurement of coronary artery dimensions are also necessary to monitor the development of care area assessment (CAA) keeping in mind that myocardial infarction is the most important cause of mortality in patients with KD¹¹.

The Covid-19 infection caused by SARS-COV-2 virus initially surfaced in December 2019 in Wuhan, China. This led to a pandemic which has resulted in over 4.5 million deaths worldwide¹². Even though the disease pattern has been reported to be significantly severe in adults, children are known to have less severe symptoms. A number of factors can be responsible for this, including a strong innate immune response, better regeneration capacity of alveolar epithelium and lack of co-morbidities in children⁴.

At the time of presentation of the first case of this series, there were approximately '3.74 million' confirmed cases of corona virus¹². The reports describing cases of Kawasaki disease with concurrent Covid-19 infection initially surfaced in April 2020². This was followed by an outburst of reported cases in Europe and USA¹³. A new phenomenon affecting children with SARS-COV-2 was described which manifested itself as a hyper-inflammatory syndrome with multi-organ involvement similar to Kawasaki Disease Shock Syndrome (Pediatric multi-system inflammatory syndrome, PMIS)³. This disease was different from the classical Kawasaki Disease since it affected older children (>5 years). Further comparison with Kawasaki Disease showed the presence of clinical features like prominent abdominal symptoms, hypotension and shock in MIS-C. In addition, a higher frequency of complications including Myocarditis and Pericarditis seemed to be associated with this disease. While in Kawasaki Disease a raised CRP and/or ESR, increased ALT, WBC and platelets (>450,000) and a decreased albumin are considered important laboratory findings, MIS-C also shows an elevation of fibrinogen, procalcitonin, D-dimers, ferritin, LDH or Interleukin 6. Poor prognosis is indicated by age greater than 5 years and an elevated ferritin level (>1400ug/L)⁸.

Management of the patients with MIS-C is based on lower treatment threshold since the long-term risk of coronary aneurysm is still unknown. Children who are sick and have cardiac and pulmonary complications should be admitted in the hospital preferably in an intensive care unit. Cardiac function should be assessed immediately with echocardiography and a close follow-up should be maintained⁵. Drug therapy in case of MIS-C is similar to that employed in Kawasaki Disease including intravenous immunoglobulin, steroids, anti-coagulation and anti-platelet therapy, immunomodulators (used in refractory cases). Anti-viral drugs like remdesivir have an uncertain role possibly because MIS-C likely represents a post-infectious complication rather than an active infection. A multidisciplinary team consisting of pediatric infectious disease, cardiology, immunology, rheumatology, hematology and intensive care specialists can be appointed based on the patients' clinical condition and multi-systemic involvement¹³.

According to the Centers for Disease Control and Prevention (CDC) report from February 2021, there are an estimated 2060 cases of multisystem inflammatory syndrome in children globally in multiple countries¹⁴. CDC recommends that "as the Covid-19 pandemic continues, with the number of cases increasing in many jurisdictions, health care providers should continue to monitor patients to identify children with a hyper-inflammatory syndrome with shock and cardiac involvement"¹⁵. This formed the basis of our decision to send a Covid-19 PCR for all the patients admitted with the symptoms indicating Kawasaki disease. Among those one was negative, second had a negative PCR but positive Covid serology (IgG), the third one presented as a recovered case of Covid-19 with a relapse of Kawasaki Disease and the fourth had a positive Covid PCR. None of these patients had any respiratory complaints and were able to maintain oxygen saturation at room air. They were all discharged without any complications.

CONCLUSION

The patients presenting with symptoms similar to Kawasaki Disease (KD) showed an association with Covid-19 in the form of positive test results (PCR and serology). However compared to various studies no significant multi-systemic involvement was seen. None of the patients mentioned above had any severe complications however; the information linking Kawasaki Disease association with coronavirus is anecdotal. Thus, with new information surfacing every day it still needs to be considered when encountering patients showing symptoms of KD. Further clarification regarding the exact pathophysiology behind the associated between SARS-COV-2 and Kawasaki disease awaits further research and investigation.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

PATIENT CONSENT

Consents were obtained for the study.

AUTHORS' CONTRIBUTION

RM collected and analyzed the patient data and wrote the manuscript; SE conceived the idea and approved the final manuscript.

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