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Spectrum of Post Covid-19 Manifestations in Children: A Case Series

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Abstract

Background: Multisystem Inflammatory syndrome in Children (MIS-C) is a common diagnosis among children in the post Covid-19 era, which usually presents with fever and varied systemic manifestations. BCG vaccination site reaction as a manifestation of MIS-C is barely ever documented. In this series, we present a rare such case report along with the other six other cases.

Case presentations: Seven cases with MIS-C are presented with four male and three female children. The median age of presentation was 3 (range: 0.4-14) years. Fever was the most common (100%) symptom followed by muco-cutaneous manifestation (50%, 4/7), as well as gastrointestinal (37.5%, 3/7), and cardiovascular symptoms (37.5%, 3/7). The clinical features which led to the diagnosis include BCG site vaccination, erythema multiforme, periungual and perineal peeling, unilateral knee joint effusion, skin scalding syndrome, urticaria, and acute glomerulonephritis. The initial work-up for fever did not yield any cause, except for a non-specific elevation of inflammatory markers. 6 cases had elevated anti-SARS-Co-V2 antibody titres with a negative RTPCR/RAT test and 1 case yielded positive RTPCR for covid status for acute infection. 2D Echocardiography showed Coronary artery dilatation in two patients which resolved on follow-up. All the patients responded well to intravenous immunoglobulin and methylprednisolone combination therapy with antiplatelet drugs.

Conclusion: BCG vaccination site reaction could occur due to antigen-homology. Cardiovascular manifestations (coronary artery dilatation) without hemodynamic instability may also be a manifestation of MIS-C, thereby placing 2D-Echo as an important step in diagnostic workup.

Key Words: Covid-19 infection, Multisystem inflammatory syndrome in Children, SARS-Co-V2, SARS-Co-V2, coronary artery aneurysm, Kawasaki disease.

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1- INTRODUCTION

The covid-19 pandemic due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) began from Wuhan city of Hubei province in China in December 2019 (1). Till date, globally, this pandemic has caused over 630 million cases and 6 million deaths (2).

In contrast to the adults wherein the disease usually manifests as respiratory failure during the second week of illness and in occasional cases as cardiovascular catastrophe, the disease severity in children usually takes the form of an asymptomatic infection or a milder form (1). This could probably be due to a higher innate immune response in the upper respiratory tract of children conferring a relative protection against serious disease (3).

By the month of April 2020, after 4 months into the pandemic, it was observed that a hyper-inflammatory syndrome manifested in children as an initial febrile period followed by a multi-system disease comprising mainly gastrointestinal system at the time of presentation and progressed to involve cardiovascular, respiratory, and muco-cutaneous systems. This was called Multisystem Inflammatory Syndrome in Children (MIS-C) by the WHO (https://emergency.cdc.gov/ han/ 2020/ han00432.asp). The estimated prevalence of MIS-C seems to be around 1 case per 3000 children (4). The disease usually manifests 4-6 weeks following a covid-19 infection in children aged 6-12 years, characterized by prolonged fever, rash, abdominal pain, and rarely shock due to cardiovascular dysfunction. There is higher prevalence of cardiorespiratory involvement, cardiovascular without respiratory, Kawasaki disease like manifestation in MIS-C as opposed to that of Covid-19 infection (5).

A recently published systematic review of MIS-C cases from India also shows similar patterns of involvement and outcome (6). In this case series, we present cases which fulfilled the criteria for MIS-C and had an atypical feature at presentation or during the course of illness which is barely reported in published literature.

2- CASE SERIES

The present case series includes seven patients (4 males and 3 females) with a median age of 3 (range: 0.4-14) years at presentation. The most common symptom at presentation was fever (100%, 7/7), mucocutaneous manifestation (50%, 4/7), and gastrointestinal symptoms (37.5%, 3/7). Cardiovascular involvement was seen in three cases (37.5%), and evidence of coagulopathy and shock/hypotension in one patient each. The demographic characteristics and clinical features of the patients are mentioned in Table 1.

a) Case 1: A seven-and-a-half-month-old male child presented with a history of cough, fever and cold for 3 days. He had respiratory distress in the form of tachypnoea with decreased air entry over the left mammary area. Chest X ray showed diffuse bilateral parenchymal haziness with hyperinflation suggestive of bronchiolitis (Fig. 1A) and hence was started on humidified oxygen. Laboratory findings including complete hemogram and inflammatory markers are reported in Table 2. The child continued to have fever spikes of 101-104^{0}F. Routine evaluation for fever with dengue, malaria, Weil-Felix, Covid-19 Rapid Antigen Test (RAT) and RTPCR, blood, and urine cultures were negative. On day 3 of admission, he had 2 episodes of vomiting followed by localized erythema with peeling of skin at BCG vaccination site (Fig. 1B). A diagnosis of MIS-C was made. Cardiovascular evaluation revealed a small ASD with 2D Echocardiography and elevated D-Dimer levels with normal electrocardiogram (ECG) and troponin-I levels. He was started on intravenous (i.v)

methylprednisolone (2 mg/kg/day), subcutaneous (s.c) low molecular weight heparin (LMWH) (2 mg/kg/day), and aspirin (5 mg/kg/day). The child started responding with temperature returning to the baseline. Anti-SARS Co-V2 antibody titres were (42.7 U/ml) elevated and the diagnosis of MIS-C was confirmed. The patient was started on 2g/kg of intravenous immunoglobulin (IVIG). He was shifted to an equivalent dose of oral prednisolone and tapered over the next 5 days. Repeated D-dimer level was 615 ng/ml at the time of discharge and the patient was advised to follow-up with 2D echocardiography. Reduction in the size of BCG vaccination site was noted (Fig. 1C).

b) Case 2: A 6-year-old male child was brought with complaints of fever, pain in abdomen, vomiting, and puffiness of face for 5 days. Illness was associated with erythema multiforme (Fig. 1F and G) in the form of symmetrical, red, raised, maculopapular lesions with occasional blistering involving both upper and lower limbs for 3 days. The parents also noticed passage of cola coloured urine 2 days prior to the presentation. On examination, the patient had scalp edema and periungual desquamation. Blood pressure was between 50^{th} to 90^{th} centile for the age and normal. Urine routine and microscopy showed red cell casts without pus cells or bacteria. Work-up for post-streptococcal glomerulonephritis (C3, C4 complement levels and anti-streptolysin-O titre) was negative. Routine fever profile as mentioned in case 1 was negative and the laboratory findings are mentioned in Table 2. He was started on ceftriaxone and doxycycline for broad spectrum coverage and levocetirizine for skin manifestations. Initial nasopharyngeal swabs for Covid-19 RAT and RT-PCR were negative; however, anti-SARS Co-V2 antibody titres obtained on day 5 of admission (154.1 IU/ml) were significantly raised. 2D Echocardiography was normal. A diagnosis of MIS-C was made and he was started on IVIG (2gm/kg) and i.v methylprednisolone (30 mg/kg). There was significant improvement in terms of absent fever spikes and resolution of haematuria after 3 days. The patient was discharged on tapering doses of oral prednisolone and aspirin (5 mg/kg/day) for 6 weeks.

c) Case 3: A 5-month-old female infant was brought by her parents with a history of fever, cough, and diarrhoea for 3 days having had a significant antecedent viral exanthem fever with rash (distributed over hands, foot, trunk, and perineal region) 2 weeks prior to the present episode. On examination, she had tachycardia and respiratory distress in the form of tachypnoea, chest retractions, and decreased air entry on the left side. Skin peeling around the hands predominantly involving periungual areas were noted (Fig. 1D, 1E). Other areas involved were foot, hand and perineal regions. Blood pressure and CRT were normal with optimal feed intake. Chest X ray showed hyperinflation with mild haziness in the bilateral lower zone. A diagnosis of acute gastroenteritis with some dehydration and lower respiratory tract infection was made.

Initially, empirical broad-spectrum antibiotics, nebulisations with bronchodilator and normal saline, humidified nasal oxygen were administered along with oral rehydration therapy. Despite the above measures, the patient had persistent tachypnoea with a respiratory rate of >60 cycles/minute. Therefore, nasal Continuous Positive Airway Pressure (CPAP) was initiated. As the patient continued to run multiple fever spikes (maximum 103^0F) with persistent tachypnoea not responding to CPAP and broad-spectrum antibiotics, diagnosis of MIS-C was considered. The laboratory evaluation consisting of fever profile, urine and blood culture, Covid-19 RAT and RTPCR were all negative except for

the inflammatory markers (ESR and CRP) which were mildly elevated (Table 2). However, anti-SARS Co-V2 antibody titres obtained on day 5 of admission were raised to 20 times the control values. 2D Echocardiography was suggestive of a left coronary artery dilatation with a Z-score of +3.2 SD. The diagnosis of MIS-C was established and treatment with IVIG (2gm/kg), pulse therapy of methylprednisolone (30 mg/kg), and aspirin (80mg/day for 5 days) was initiated. After 5 days, the patient was discharged with tapering doses of oral prednisolone and low dose aspirin (5 mg/kg/day) for 4 weeks. A follow-up 2D Echo, 4 weeks after discharge, showed a decrease in coronary artery dilatation size (+2.4SD). She is under active surveillance.

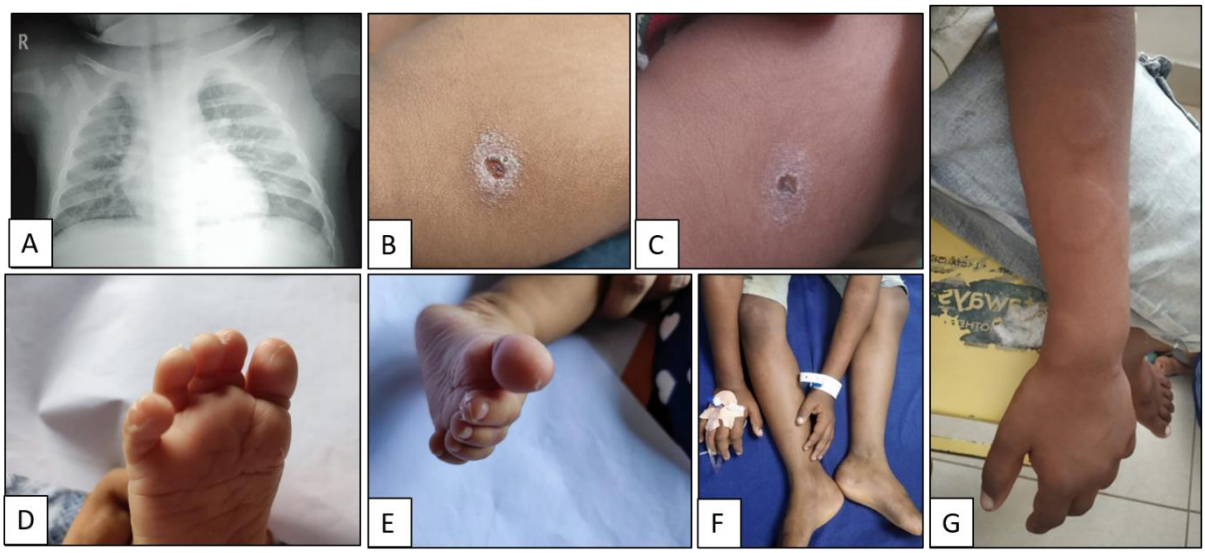

Fig 1: Chest X ray and general skin manifestations

d) Case 4: A 10-year-old male presented with fever for 12 days and cough, loose stools, and right knee joint pain of 4 days duration. On enquiry, there was no recent past history of skin/throat infection. Clinical examination revealed erythema and decreased joint mobility secondary to tenderness was noted. On auscultation of the respiratory system bilateral normal vesicular breath sounds were present. Diagnostic workup for rheumatic fever and reactive arthritis (antistreptolysin O titre, ECG and cardiac biomarkers, urine/stool culture, chest X ray) was negative. USG of the knee joint was suggestive of effusion with increased joint space. Detailed work ups for the cause of fever (malaria, dengue, leptospirosis, Weil-Felix) were negative. Ceftriaxone was started in view of persistent fever spikes along with oral rehydration, bronchodilators, and mucolytics for symptomatic relief.

Persistent symptoms despite the above measures directed us towards considering MIS-C as diagnosis and further evaluation for past/present COVID-19 infection showed elevated anti SARS CoV-2 antibodies with negative RAT and RTPCR shown in Table 2. Additionally, 2D echocardiography showed left coronary artery dilatation with normal systolic/diastolic functions and valves. The patient was started on IVIG (2gm/kg), pulse therapy of MPS (30 mg/kg) for 3 days after which oral prednisolone was continued for 5 days and tapered over the next 4 weeks along with low dose aspirin (5mkd). The child was lost to follow up.

e) Case 5: A 1-year-old girl presented with a 4 days history of fever and generalised bilaterally symmetrical skin scalding over face, neck, chest, abdomen, upper limbs, and thighs for 2 days.

There was an associated history of cough for 2 days. Examinations showed erythematous and skin peeling with positive Nikolsky sign in the above mentioned sites without any signs of pneumonia. Baseline evaluations are presented in Table 2.

The child was started on Amoxiclav and Clindamycin. Skin swabs sent for microscopy and culture did not show any growth. Due to negative fever profile (malaria, dengue, Weil-Félix, Covid-19 RAT negative /RTPCR was positive, leptospirosis, blood, and urine culture) and persistent symptoms even after 3 days, antibiotics were upgraded to intravenous vancomycin.

Considering a diagnosis of MIS-C, the same Covid antibodies were sent on day-10, which were significantly raised. Screening 2D Echocardiography was normal. The patient was started on IVIG (2gm/kg), pulse therapy of MPS (30 mg/kg) for 3 days after which oral prednisolone was continued for 7 days and tapered over the next 4 weeks along with low dose aspirin (5mkd).

f) Case 6: A 14-year-old male child presented with fever for 5 days and itchy skin lesions for 3 days. They were associated with loose-stools for 4 days. On examination, diffuse urticaria on upper limbs, chest, and trunk was observed. He was diagnosed with urticaria and started on levocetirizine. The baseline laboratory evaluations are mentioned in Table 2. Azithromycin and amoxiclav were started due to the persistent fever and a negative fever profile. However, the titres of Covid-19 antibody were markedly elevated (2500 IU/ml) pointing to a diagnosis of MIS-C. The patient received IVIG (2gm/kg) and MPS (30 mg/kg) for 3 days and tapered over 2 weeks. He also received low dose aspirin (5mkd) for 4 weeks.

g) Case 7: A 3-year-old female child presented with complaints of fever for 5 days associated with the passage of cola coloured urine, oliguria, and generalized edema for 2 days. Blood pressure was between 50^{th}-90^{th} centile for the age. A diagnostic workup for acute infectious glomerulonephritis (C3, C4 complement levels, antistreptolysin-O titre, and urine routine/microscopy) was negative. Rest of the biochemical parameters including blood/urine cultures are mentioned in Table 1. The child continued to run fever spikes despite having passed 3 days of amoxiclav to cover the streptococcal group of organisms. A complete fever work-up was negative except for a significantly elevated Covid-19 antibody titre (804.1 IU/ml) as shown in Table 2. Screening 2D echo study was normal. The diagnosis of MIS-C was made and she was started on IVIG (2g/kg) and MPS (30 mg/kg) for 3 days and tapered over 3 weeks. He also received aspirin (5mkd) for 4 weeks.

3- DISCUSSION

Over a period of time, the post covid sequelae in the form of multisystem inflammatory syndrome in children have been revised in terms of case identification, case definition and approach to management of the disease. Since late April 2020 the number of cases of MISC has increased dramatically with significant morbidity and mortality (7).

Here we described 8 cases with atypical manifestations as post covid sequelae which presented to us as BCG site reactivation, erythema multiforme, periungual and perineal desquamation, joint effusion, covid scalded skin syndrome, urticaria, and acute glomerulonephritis.

Table-1: Characteristic features of MIS-C in our cohort

WHO diagnostic criteria for MIS-C	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age	6 months	7 Years	6 months	10 years	1 Year	14 years	1 Year
Fever >3 days	+	+	+	+	+	+	+
Rash or bilateral non-purulent conjunctivitis or muco-cutaneous inflammation signs	+	+	–	–	+	+	–
Shock/ hypotension	–	–	–	–	–	–	+
Features of myocardial dysfunction, pericarditis, valvulitis, or coronary abnormalities	–	+	+	+	–	–	–
Evidence of coagulopathy	+	–	–	–	–	–	–
Acute gastrointestinal problems	–	–	+	+	–	–	+
Atypical feature of presentation	BCG site reactivation	Erythema multiforme	Periungual and perineal peeling	Knee joint swelling with tenderness	Diffuse skin scalding	Urticaria	Glomerul onephritis

Table-2: Laboratory features of MIS-C patients in our cohort

Variable	Reference range	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Hb (g/dl)	11.4-14.7	9.2	13.9	11.8	12.8	11.9	11.7	11
TLC (cells/mm3)	4400-12900	15620	10080	18680	18650	7450	4710	9590
Platelets(cells/mm3)	2.5-5x105	3.58x105	3.06x105	5.8x105	4.08x105	3.08x105	1.41x105	1.0x105
Na (mEq/L) K (mEq/L)	132-141 3.5-5.8	142 3.8	138 4.7	140 5	138 4.2	135 4.6	138 4.7	138 3.5

Variable	Reference range	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Cl (mEq/L)	102-112	97	97	97	102	101	98	101
AST/ALT (U/L)	21-44 9-25	84/102	42/43	54/31	48/30	52/31	48/86	46/29
Albumin (mg/dl)	3.5-5	2.8	3.2	3.6	3.2	2.4	3.5	2.8
Creatinine (mg/dl)	0.1-0.7	0.49	0.43	0.64	0.45	0.40	0.66	0.45
BUN (mg/dl)	3-18	15	23	08	08	21	18	10
CRP (mg/dL)	0.01- 10.41	42.8	58	17.4	136	86	98	180
ESR (mm/at 1 hour)	0-10	56	4	34	42	28	30	44
PT (seconds) aPTT (seconds) INR (-)	10.2-12.1 24-37 -	12 26 0.8	12 24 0.9	13 30 0.8	12 28 0.9	13 24 0.9	12 25 1.0	12 22 0.9
LDH (U/L)	163-321	1845	349	1896	956	1352	986	1250
D dimer (ng/ml)	<500	1345	132	365	148	225	289	312
2d echo findings		Small ASD with normal coronary arteries	Normal study	Left coronary artery dilatation with Z Score of +3.2 SD	Left Coronary artery dilatation	Normal study	Normal study	Normal study
COVID RAT/RTPCR Nasopharyngeal PCR		Negative	Negative	Negative	Negative	Positive	Negative	Negative
Covid antibody(U/ml)		29.6 <0.8u/ml-neg >0.8u/ml-positive	154.1 <0.8u/ml-neg >0.8u/ml-positive	48.5 <1 u/ml-neg >1 u/ml-positive	364.6 <0.8u/ml-neg >0.8u/ml-positive	108.4 <0.8u/ml-neg >0.8u/ml-positive	2500 <0.8u/ml-neg >0.8u/ml-positive	804.1 <0.8u/ml-neg >0.8u/ml-positive

Earlier MISC was believed to be an atypical manifestation of Kawasaki disease- a medium sized vessel vasculitis which usually manifests with fever, mucocutaneous rash, non-purulent conjunctivitis, cervical adenopathy and edema erythema of skin with inflammatory manifestation of extremities in young children and late cardiovascular sequelae like coronary artery aneurysm (8).

MISC is identified clinically as a disordered immunological response following SARS-CoV-2 infection. The pathophysiology associated with this is described as a post-infectious phenomenon related to IgG antibody-mediated enhancement of disease. This is supported by the facts that MIS-C cases have lagged in time compared with the peak of SARS-CoV-2 infection in many countries and evidence of prior covid infection has been proven by the increased titre of covid antibodies with a negative rapid antigen and nasopharyngeal assays with PCR tests (9).

In the present case series, all patients were presented with features of fever and involvement of ≥2 systems with raised inflammatory markers. The atypical manifestations in each case have already been described.

The median age (3 years) of presentation in our cohort was younger than that described elsewhere and multiple systematic reviews report a median age of 5-10 years (10).

Though the spectrum of manifestations vary, persistent fever underscores the presentation as defined by WHO in all the cases as in our case series. (https://www.who.int/publications-detail/multisystem-inflammatorysyndrome-in-children-and-adolescents-withcovid-19).

Muco-cutaneous manifestations are among the most common manifestations at presentation in MISC (6, 10). Similarly in our series it was the most common symptom associated with fever. Diffuse, nonspecific eruption, dry and red lips and/or other mucosal changes, hand and feet erythema and edema form the top four dermatological findings of MIS-C (11). Apart from the three cases (cases 2, 5, and 6), presented with previously described skin/mucous system manifestation, we observed a focal BCG site reactivation in case 1. Though BCG vaccination site erythema is described in Kawasaki disease and in the following m RNA vaccines for Covid-19, till date, there is just a single case report as a feature of MIS-C which is an atypical feature (12, 13). The previously described case could still be Kawasaki disease (KD) with coincidental SARS-Co-V2 infection, since there were evident cardiovascular manifestations and other diagnostic evidence of KD. Considering the absence of diagnostic criteria for KD, this could probably be the first such case. The underlying pathogenesis is probably due to the antigen homology between envelope protein of SARS-Co-V2 and the mycobacterium. In addition, the use of non-Japanese (French and Danish) strains for vaccination in India demonstrates that a lower antigenic dose might also cause immunological cross reaction in MIS-C (13).

The cardiovascular manifestations predominantly seen in our series were the echocardiographic manifestations in the form of coronary artery dilatation in two cases (28%, 2/7) with a significant decrease in the dilatation score on follow-up in one case, thus hypothesizing a causal relationship. A similar prevalence of 28% was also seen in a systematic review of 313 patients from India (6). We did not see any patients with ECG abnormalities and systolic/diastolic dysfunctions which clinically correlate with the absence of cardiogenic shock in our case series. Contrastingly, previous studies have

shown ECG abnormalities in 35% and right/left ventricular dysfunction in 30-40% of patients[10]. However, since the complete cardiac biomarkers (troponin I, B-type natriuretic peptide, and N-terminal pro-B type natriuretic peptide levels) were not available in all cases, subclinical myocardial injury might have been underestimated.

The clinical features of acute Covid-19 and MIS-C generally overlap. However, organ system involvement and differing patterns of presentation may help differentiate both of the entities. Occurrence in younger age, without underlying medical comorbidities, and multiple organ involvement with greater elevation of inflammatory parameters (CRP, ferritin, D-dimer) points towards the latter (14). In the presence of severe manifestations, it is important to consider/rule out alternative diagnoses such as Kawasaki disease and Toxic shock syndrome by appropriate case definitions.

The cornerstone of MIS-C management includes suppression of the underlying inflammatory response. Various agents used include IVIG, high dose systemic glucocorticoids, and biological immune-modulatory molecules. All cases in the present series were successfully treated with IVIG, methylprednisolone, and aspirin as per the institutional standard of care; and no patient had mortality. Previously published studies also have used IVIG as the most common modality of treatment (65-80%) of cases followed by intravenous glucocorticoids (50-70%) in addition to anticoagulation therapies (1, 10). Additional immunomodulatory therapies such as interleukin-6 inhibitors (tocilizumab or siltuximab), interleukin-1Ra inhibitor (anakinra), and anti TNF-alpha monoclonal antibody (infliximab) have been used in minority of the cases. The use of IVIG and MPS combination therapy is supposed to be better than either of the treatments alone (15). Mortality rates in previously described series with MIS-C range from 0 to 2% (5).

4- CONCLUSION

In the present case series, we have presented seven cases of MIS-C with atypical features at presentation without profound cardiovascular involvement along with the Second BCG vaccination site rash. Combination of IVIG and methylprednisolone pulse therapy followed by oral glucocorticoids was revealed to be an effective treatment modality.

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