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ORIGINAL ARTICLE

Initial Immunomodulation and Outcome of Children with Multisystem Inflammatory Syndrome Related to COVID-19: A Multisite Study from India

Narendra Kumar Bagri[1] · M. Khan[2] · R. M. Pandey[2] · Rakesh Lodha[1] · S. K. Kabra[1] · MIS-C study group

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Abstract

Objective To determine the outcomes in children with MIS-C receiving different immunomodulatory treatment.

Methods In this multicentric, retrospective cohort study, data regarding treatment and outcomes of children meeting the WHO case definition for MIS-C, were collected. The primary composite outcome was the requirement of vasoactive/inotropic support on day 2 or beyond or need of mechanical ventilation on day 2 or beyond after initiation of immunomodulatory treatment or death during hospitalization in the treatment groups. Logistic regression and propensity score matching analyses were used to compare the outcomes in different treatment arms based on the initial immunomodulation, i.e., IVIG alone, IVIG plus steroids, and steroids alone.

Results The data of 368 children (diagnosed between April 2020 and June 2021) meeting the WHO case definition for MIS-C, were analyzed. Of the 368 subjects, 28 received IVIG alone, 82 received steroids alone, 237 received IVIG and steroids, and 21 did not receive any immunomodulation. One hundred fifty-six (42.39%) children had the primary outcome. On logistic regression analysis, the treatment group was not associated with the primary outcome; only the children with shock at diagnosis had higher odds for the occurrence of the outcome [OR (95% CI): 11.4 (5.19–25.0), $p < 0.001$]. On propensity score matching analysis, the primary outcome was comparable in steroid ($n = 45$), and IVIG plus steroid ($n = 84$) groups ($p = 0.515$).

Conclusion While no significant difference was observed in the frequency of occurrence of the primary outcome in different treatment groups, data from adequately powered RCTs are required for definitive recommendations.

Keywords COVID-19 · IVIG · MIS-C · Outcome · Propensity scoring · Resource-poor setting, Steroids · Treatment modality

Introduction

Multisystem inflammatory syndrome in children temporally associated with SARS-CoV-2 (MIS-C) has emerged as a global child health issue. Various scientific bodies like the CDC, RCPCH, and WHO released their guidance documents in this context during April–May 2020 [1–3]. After the early reports from Italy, documenting a spurt in cases presenting with Kawasaki disease–like spectrum, hundreds of publications across the globe including India described similar features [4–6]. The novelty of this disease poses many challenges in formulating the treatment guidelines. Given the similarity of MIS-C with Kawasaki disease and the macrophage activation syndrome complicating many rheumatic disorders, intravenous immunoglobulin (IVIG) and steroids formed the sheet anchor for MIS-C management. Early guidance for management of MIS-C from the American College of Rheumatology advocated immunomodulation using IVIG and steroids, and anakinra for refractory cases [7]. However, there is lack of high-quality evidence to guide the choice of initial therapy in MIS-C.

Further, the nature of the disease poses a challenge in conducting randomized controlled trials to generate a high level of evidence. One pragmatic approach is to analyze the available data from observational studies using various statistical techniques such as propensity score matching, as has been done in recent studies [8–10]. However, these data are mainly from developed nations. The developing world

Narendra Kumar Bagri and M. Khan are joint first authors.

✉ Rakesh Lodha
rakesh_lodha@hotmail.com

[1] Department of Pediatrics, All India Institute of Medical Sciences, New Delhi 110029, India

[2] Department of Biostatistics, All India Institute of Medical Sciences, New Delhi, India

settings are challenged with multiple factors such as cost constraints with the use of IVIG, non-availability of biologics like anakinra, and the high background rate of infections with overlaping features similar to MIS-C.

In the present work, the data of children with MIS-C from seventeen centers across India were collated and analyzed to compare the outcome in the different treatment arms (IVIG alone, IVIG plus steroids, and steroids alone).

Material and Methods

This retrospective cohort study is an analysis of data collected from different participating centers in India. A formal invitation to participate in the study through email was sent to 21 centers, of which seventeen sites participated in this study. The Institute Ethics Committee approved the study of the coordinating site (IEC-487/02.07.2021). All participating centers also obtained ethical clearance from their respective ethics committees.

A data extraction form was developed and shared with all participating sites and finalized after inputs from all. The information about the demographic profile, clinical features, criteria for diagnosis of MIS-C, laboratory investigations, treatment received (including details of immunomodulatory treatment: IVIG / steroids / IVIG + steroids / biological, vasoactive drugs, and respiratory support) and the outcome was sought. The data from each center were collected by one of the treating physicians at each site. The data were entered in a predesigned form using MS Access or MS Excel, circulated from the coordinating site. Data from one center were received in hard copy, which was later, filled in the Excel sheet. Data from various sites were merged; if any difference in the units of laboratory variables was found, those were modified to standard units for uniformity. The outcomes of interest were calculated from the data provided. The de-identified data of children with MIS-C as per WHO case definition [3], admitted (between April 2020 and June 2021) at participating centers were eligible for inclusion in the study. The subjects for whom the data pertaining to the primary outcome were missing, were excluded from this study.

Based on the immunomodulatory treatment received, the patients were categorized into four groups: IVIG alone; steroids alone; IVIG plus steroids; and one group where patients did not receive immunomodulation.

The primary outcome was the requirement of vasoactive/inotropic support on day 2 or beyond or need of mechanical ventilation on day 2 or beyond after initiation of immunomodulatory treatment or death during hospitalization in the treatment groups. The baseline cardiac outcomes (ejection fraction, coronary dilation/aneurysm) in different treatment groups were also compared. The coronary aneurysms were defined as per coronary size estimations using the standard norms [11].

Data were entered in a Microsoft Access or MS Excel forms by each of the participating centers. Data were collated by the coordinating center and checked for missing data and formatting. RL and NKB screened the data for accuracy and completeness, and the respective sites were contacted in case of any discrepancies. The cleaned dataset was analyzed using Stata software (StataCorp, College Station, TX). Descriptive statistics were used to summarize parameters in the treatment groups. The outcomes in the treatment groups were compared. Logistic regression analysis was performed to adjust for the differences in the baseline features of the subjects for predicting the primary outcome. A propensity score matching analysis was also performed to match the possible confounding factors which might influence the outcome. Given the limited numbers in the IVIG alone arm, outcomes were compared in the two groups: steroid alone vs. IVIG plus steroid. The details of the methods for propensity score matching analysis are provided in Supplementary material S1.

The patients or public were not involved in the design, or conduct, or reporting, or dissemination plans of the present research.

Results

The seventeen participating sites provided data on children diagnosed with MIS-C between April 2020 and June 2021. The data of 368 subjects meeting the WHO case definition for MIS-C were analyzed for the outcome comparisons.

Of the 368 subjects, 28 received IVIG alone, 82 received steroids alone, 237 received IVIG and steroids, while 21 did not receive any immunomodulation. Among children who received steroids in any of the groups, the type of steroid was mentioned in 281 records; 255 (90.4%) received intravenous methylprednisolone, 18 (6.4%) oral prednisolone, while 8 (2.8%) received dexamethasone. Six children received tocilizumab.

Table 1 summarizes the demographic, laboratory, and treatment details of the study population categorized by the immunomodulatory treatment received. The mean (SD) age of the study population was 80.2 (51.1) mo, majority (62.9%) being boys. In addition to fever, which was universal in all subjects, gastrointestinal symptoms, rash, and shock were the other common presenting features reported in 70.3%, 58.3%, and 53.5% of the subjects, respectively. In this cohort, 225 (61.1%) children received vasoactive/inotropic drug support, while 67 (23%) were mechanically ventilated. The median (IQR) duration of hospital stay was 8 (6, 11) d. Patients who received IVIG alone were significantly

Table 1 Comparison of demographic characteristics in various treatment groups

	IVIG alone ($n = 28$)	Steroids alone ($n = 82$)	IVIG + steroids ($n = 237$)	No immunomodulation ($n = 21$)	p value
Age (months), median (IQR)	51 (14.5, 84)	80.5 (30, 132)	84 (48, 75)	60 (30, 96)	0.03
Height/Length, cm, mean (SD)	110.99 (30.4) ($n = 15$)	111.72 (30.9) ($n = 62$)	114.10 (28.3) ($n = 190$)	105.62 (28.13) ($n = 16$)	0.43
Gender, males, *n* (%)	18 (64.3)	45 (54.9)	153 (64.5)	13 (61.9)	0.53
Comorbidity, *n* (%)	3 (10.7)	20 (24.4)	21 (8.9)	6 (28.6)	0.003
SARS-CoV-2 PCR/RAT positive, *n* (%)	8 (28.6)	19 (23.2)	69 (29.1)	8 (38.1)	0.54
COVID antibody positive	17 (60.7)	60 (73.2)	18 (79.3)	14 (66.6)	0.22
Rash, *n* (%)	17 (60.7)	38 (46.3)	150 (63.3)	8 (38.1)	0.03
Gastrointestinal involvement, *n* (%)	19 (67.85%)	57 (69.5)	166 (70.0)	16 (76.2)	0.94
Shock, *n* (%)	8 (28.6)	30 (36.6)	140 (59.1)	9 (42.8)	0.02
Altered sensorium, *n* (%)	7 (25)	20 (8.9)	54 (22.9)	5 (23.8)	0.98
Respiratory symptoms, *n* (%)	14 (50)	28 (34.1)	107 (45.1)	8 (38.1)	0.222
Cardiac involvement (either laboratory/ECHO), *n* (%)	18 (64.3)	26 (31.7)	175 (73.8)	3 (14.9)	< 0.001
LVEF at baseline, %, mean (SD)	57.9 (4.7) ($n = 18$)	58.4 (9.1) ($n = 61$)	51.3 (12.4) ($n = 156$)	61.2 (3.7) ($n = 12$)	0.02
Duration of fever/illness	6 (5, 8)	6 (5, 8)	5 (4, 7)	5 (3, 7)	0.10
Duration of hospital stay, median (IQR)	9 (6, 13)	7 (5, 13.5)	8 (6, 10)	6 (4, 8)	0.1
Hemoglobin (g/dL), mean (SD)	11.3 (3.8)	10.4 (2.1)	10.1 (2.1)	10.2 (2.4)	0.08
Total leucocyte counts (/mm^3), median (IQR)	12400 (6000, 15700)	11800 (6800, 14500)	10900 (7480, 15100)	9970 (6655, 18795)	0.98
Lymphocyte count (/mm^3), median (IQR)	2639 (970, 3598)	2389 (1343, 4380)	1880 (960, 3705)	2600 (1587, 5300)	0.24
Platelet count ($\times 10^5$/mm^3), median (IQR)	2.3 (1.2, 4.3)	1.8 (1.1, 1.8)	1.4 (0.8, 2.4)	2.28 (1.3, 3.5)	0.004
ESR (mm/h), median (IQR)	53.5 (32, 65)	48 (36, 57)	45 (30, 72)	36 (18, 49)	0.41
CRP (mg/L), median (IQR)	64.15 (21, 162)	65 (20.91, 143)	90 (40, 145)	13.7 (3.4, 37)	0.0001
Serum ferritin ng/mL, median (IQR)	565.15 (205, 766)	573.95 (172, 1356.5)	657.5 (319, 1201)	249.9 (106.5, 443.1)	0.022
NT-proBNP (pg/mL), median (IQR)	1200 (120, 1500)	1890 (49, 6023)	1600 (457, 4631)	296.5 (49, 4884.8)	0.57
D-dimer (ng/mL), median (IQR)	1983 (500, 5100)	1687.5 (24.8, 3500)	1481 (500, 3510)	1051 (527, 5056)	0.9

CRP C-reactive protein, *ESR* Erythrocyte sedimentation route, *IQR* Interquartile range, *IVIG* Intravenous immune globulin, *LVEF* Left ventricular ejection fraction, *NT-proBNP* N-terminal pro b-type natriuretic peptide, *PCR* Polymerase chain reaction, *RAT* Rapid antigen test, *SD* Standard deviation

younger. Those that received both IVIG and steroids had significantly lower platelet counts, and higher CRP and ferritin.

Table 2 summarizes the baseline cardiac parameters. The mean ejection fraction at baseline was significantly lower in the group receiving both IVIG plus steroids than other treatment groups. Seven children had coronary dilation at baseline, while 25 had coronary aneurysms; there was no difference in the observed frequency of these aneurysms among the various treatment arms.

Forty (10.9%) children succumbed during the hospital stay. The primary outcome occurred in 156 (42.4%) children. The primary outcome occurred more often in the group receiving both IVIG plus steroids ($p = 0.027$) (Table 3).

On logistic regression analysis to assess the association between the treatment groups and the outcome adjusting for other factors, the treatment groups did not seem to have an effect on the primary outcome; only children with shock at diagnosis had higher odds for the occurrence of the composite outcome [OR (95% CI): 11.4 (5.19–25.0), $p < 0.001$] (Table 4). The results were similar when the outcome was compared among the three treatment groups after omitting the 'no immunomodulatory treatment' group. There was no difference in the primary outcome in the steroid, and IVIG plus steroid groups ($p = 0.1$). When the data were analyzed using propensity score analysis comparing the primary outcome in steroid ($n = 45$) and IVIG plus steroid ($n = 84$)

Table 2 Baseline cardiac parameters of the study population

	IVIG alone	Steroids alone	IVIG plus steroids	No immunomodulation	*p* value
LVEF @ baseline, % (SD) (*n* = 288)	57.9 (4.7) (*n* = 23)	58.4 (9.1) (*n* = 64)	51.3 (12.4) (*n* = 189)	61.2 (3.7) (*n* = 12)	0.0001
LCA @ baseline					0.80
Normal coronary, *n/N*	8/12	18/23	56/79	7/7	
Coronary dilation, *n/N*	1	1	5	0	
Coronary aneurysm, *n/N*	3	4	18	0	
LAD @ baseline					0.50
Normal coronary, *n/N*	4/6	17/18	38/55	6/6	
Coronary dilation, *n/N*	1/6	0/18	04/55	0/6	
Coronary aneurysm, *n/N*	1/6	1/18	13/55	0/6	
RCA @ baseline					0.36
Normal coronary, *n/N*	7/10	18/22	56/76	6/8	
Coronary dilation, *n/N*	0/10	0/22	10/76	1/8	
Coronary aneurysm, *n/N*	3/10	4/22	10/76	1/8	

IVIG Intravenous immune globulin, *LAD* Left anterior descending artery, *LCA* Left coronary artery, *LVEF* Left ventricular ejection fraction, *RCA* Right coronary artery, *SD* Standard deviation

groups, no difference was observed ($p = 0.515$) (Supplementary material S1).

Discussion

The present multicentric study from a resource-limited setting in children with MIS-C reports the effect of various therapeutic options (IVIG alone, IVIG plus steroids, and steroids alone) on the outcome. The choice of initial immunomodulation was not associated with the outcome in the present study. Children presenting with shock at diagnosis had higher odds for the occurrence of the primary outcome [OR (95% CI): 11.4 (5.19–25.0), $p < 0.001$]. The data were analyzed using propensity score analysis to compare the primary outcome in steroid and IVIG plus steroid groups. No discernible difference was observed in the outcomes ($p = 0.515$). The small number of patients in the IVIG alone group precluded us from making definitive conclusion about efficacy of this intervention.

The present findings are similar to that of the study by McArdle et al., who did not observe any difference in the composite outcome (composite of inotropic support or mechanical ventilation by day 2 or later or death) in multicentric international cohort of 614 children, among IVIG alone, IVIG and steroids, and steroids alone groups [10]. They did not observe any difference in the temporal dynamics of disease severity (inflammatory markers, escalation of immunosuppression) in the groups. Although the sequential severity of illness was not analysed in the present study, the trend seems to be unaffected by the initial immunomodulation, as inferred from the

Table 3 Outcomes in different treatment groups

	IVIG alone (*n* = 28)	Steroids alone (*n* = 82)	IVIG + steroids (*n* = 237)	No immunomodulation (*n* = 21)	*p* value
Primary outcome*, *n* (%)	12 (42.8)	25 (30.5)	113 (47.7)	6 (28.6)	0.03
Duration of inotropic support, median (IQR)	4 (2, 5)	3 (2, 5.5)	3 (2, 4)	2 (2, 4)	0.71
Duration of mechanical ventilation, median (IQR)	2 (2, 9)	4 (3, 5)	3 (2, 5)	2 (2, 2)	0.63
Death, *n*	02	10	27	01	0.82

*Inotropic requirement (requirement of vasoactive/inotropic support on day 2 or beyond or need of mechanical ventilation on day 2 or beyond after initiation of immunomodulatory treatment or death during hospitalization)

IQR Interquartile range, *IVIG* Intravenous immune globulin

Table 4 Logistic regression analysis for the association between the treatment group and primary outcome

	Odds ratio (95% CI)	*p* value
Treatment group*	0.89 (0.53–1.51)	0.67
Age (months)	1.00 (0.99–1.00)	0.86
Shock at presentation	11.4 (5.19–25.0)	< 0.0001
Antibody to SARS-CoV-2	0.86 (0.27–2.72)	0.80
LVEF at baseline	0.97 (0.94–1.0)	0.08
Total leucocyte count	1.00 (0.99–1.0)	0.36
Platelet count	1.04 (0.85–1.28)	0.69
CRP	0.99 (0.99–1.0)	0.9
Serum ferritin	1.00 (0.99–1.0)	0.89

*IVIG alone, steroids alone, IVIG plus steroids, no immunomodulation

CRP C-reactive protein, *LVEF* Left ventricular ejection fraction

comparable mean duration of inotropic support and mechanical ventilation in the different treatment arms.

On the other hand, Son et al. evaluated 518 children with MIS-C and reported that IVIG plus steroids were associated with a lower risk of cardiac dysfunction than IVIG alone [9]. Similarly, a retrospective study in a French cohort with 181 children also showed a favorable outcome in terms of early defervescence, the requirement of inotropic support, and duration of intensive care stay in the group receiving both IVIG and methylprednisolone as compared to IVIG alone [8]. However, there were differences in the predefined primary outcomes of these studies [10–12]; cardiac dysfunction or shock on or after day 2 in the study by Son et al. [9]; the persistence of fever 2 d after the introduction of initial therapy or recrudescence of fever within 7 d in the French cohort [8], compared to the composite outcome (requirement of vasoactive/inotropic support for ≥ 2 d or need of mechanical ventilation ≥ 2 d after initiation of immunomodulatory treatment or death during hospitalization), in the Best Available Treatment Study (BATS) by McArdle et al [10]. In the present study, death was also included as a primary outcome.

No difference in the outcome based on the treatment groups was observed on logistic regression analysis. Further, while using propensity score matching analysis, the outcome was comparable in the group receiving IVIG plus steroids and steroid alone, even though only two groups could be matched and that too in small numbers. This observation is of relevance given the cost and availability of IVIG. Even the recent WHO living guidance for MIS-C without Kawasaki phenotype suggests use of corticosteroids in addition to supportive care rather than either IVIG plus supportive care or supportive care alone [13]. These guidelines must, however, be viewed with the caveat that they are based on observational studies rather than randomized controlled trials.

The mortality observed in the present study subjects is strikingly higher than other large series from developed nations (10.87% vs. 1%–2%). High mortality (27.5%) has also been reported from a single-center study from India, which has not participated in the present study [12].

Although the present study was not aimed to study the predictors of mortality, the authors speculate that the high mortality in the present study settings may be attributed to poor access to tertiary care hospitals, delay in seeking care, and high background infection rates in tropical countries posing a diagnostic challenge for MIS-C. In addition, nonavailability/affordability of biological agents like anakinra and tocilizumab in resource-limited settings might also have contributed to these differences; 22/614 (3.5%) and 107/518 (20.6%) children received a biological agent in the studies by Son et al. and McArdle et al., respectively [9, 10]. In contrast, only 6 subjects received a biological in the present study.

The present study has certain limitations; most of these are due to the retrospective nature of the study. The propensity score analysis was used but the matching could be achieved only for a small proportion in two of the treatment groups. In addition, the factors, which might have influenced the decision to choose the initial immunomodulation, and thus, affected the outcome, were not assessed. The variability in the services/practices at various participating centers, such as use of vasoactive agents, tapering strategies, etc. was not studied; all the participating centers were tertiary care institutions with pediatric intensive care services. Owing to a lack of data, the number of children meeting classification for macrophage activation syndrome and long-term cardiac and coronary results were not studied. Also, the effect of different doses of steroids on the outcome was not analyzed.

Conclusion

No difference was observed in the outcomes in children with MIS-C with different immunomodulation therapies. However, more extensive studies, including adequately sized RCTs are needed to establish the best therapeutic option for managing MIS-C, particularly in resource-limited settings.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12098-022-04254-5.

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The MIS-C Study Group (in alphabetical order, equal contribution) Suresh Kumar Angurana, Department of Pediatrics, Advanced Pediatric Center, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India; Shally Awasthi, Department of Pediatrics, King George's Medical University, Lucknow, Uttar Pradesh, India; Harshita Bamnawat, Department of Pediatrics, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India; Javeed Iqbal Bhat, Department of Pediatrics, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Jammu & Kashmir, India; Tsultem D. Bhutia, Department of Pediatrics, New STNMMS Hospital, Gangtok, Sikkim, India; Bashir Ahmad Charoo, Department of Pediatrics, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, Jammu & Kashmir, India; Abhijit Choudhary, Department of Pediatrics, All India Institute of Medical Sciences, Nagpur, Maharashtra, India; Bharat Choudhary, Department of Pediatrics, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India; Rashmi Ranjan Das, Department of Pediatrics, All India Institute of Medical Sciences, Bhubaneswar, Odisha, India; Bhagirathi Dwibedi, Department of Pediatrics, All India Institute of Medical Sciences, Bhubaneswar, Odisha, India; Sanajit Ghosh, Department of Pediatrics, Medical College Kolkata, Kolkata, West Bengal, India; Meenakshi Girish, Department of Pediatrics, All India Institute of Medical Sciences, Nagpur, Maharashtra, India; Krishna Mohan Gulla, Department of Pediatrics, All India Institute of Medical Sciences, Bhubaneswar, Odisha, India; Jagdish Prasad Goyal, Department of Pediatrics, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India; Prakriti Gupta, Department of Pediatrics, All India Institute of Medical Sciences, Patna, Bihar, India; Shivanand I, Department of Pediatrics, KIMS, Hubbali, Karnataka, India; Atul Jindal, Department of Pediatrics, All India Institute of Medical Sciences, Raipur, India; Joseph John, Department of Pediatrics, All India Institute of Medical Sciences, Bhubaneswar, Odisha, India; Preetha Joshi, Department of Pediatrics, Kokilaben Dhirubhai Ambani Hospital and Medical Research Institute, Mumbai, India; Ravleen Kaur, Department of Pediatrics, Dr Rajendra Prasad Government Medical College Kangra at Tanda, Himachal Pradesh, India; Daisy Khera, Department of Pediatrics, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India; Amit Kumar, Department of Pediatrics, All India Institute of Medical Sciences, Patna, Bihar, India; Pradeep Kumar, Department of Pediatrics, All India Institute of Medical Sciences, Patna, Bihar, India; Prawin Kumar, Department of Pediatrics, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India; A. V. Lalitha, Department of Pediatric Intensive Care, St. John's Medical College and Hospital, Bangalore, Karanataka, India; Mahesh Maheshwari, Department of Pediatrics, All India Institute of Medical Sciences, Bhopal, India; Shikha Malik, Department of Pediatrics, All India Institute of Medical Sciences, Bhopal, India; Rakesh Mondal, Department of Pediatrics, Medical College Kolkata, Kolkata, West Bengal, India; Jayashree Muralidharan, Department of Pediatrics, Advanced Pediatric Center, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India; Gayatri Pawar, Department of Pediatrics, KIMS, Hubbali, Karnataka, India; Arun Prasad, Department of Pediatrics, Medical College Kolkata, Kolkata, West Bengal, India; Sunil Kumar Rao, Department of Pediatrics, Institute of Medical Sciences, BHU, Varanasi, Uttar Pradesh, India; Vinod H. Ratageri, Department of Pediatrics, KIMS, Hubbali, Karnataka, India; Mihir Sarkar, Department of Pediatrics, Medical College Kolkata, Kolkata, West Bengal, India; Amit Kumar Satpathy, Department of Pediatrics, All India Institute of Medical Sciences, Bhubaneswar, Odisha, India; Jhuma Sankar, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi 110029, India; Seema Sharma, Department of Pediatrics, Dr Rajendra Prasad Government Medical College Kangra at Tanda, Himachal Pradesh, India; Ankur Singh, Department of Pediatrics, Institute of Medical Sciences, BHU, Varanasi, Uttar Pradesh, India; Kuldeep Singh, Department of Pediatrics, All India Institute of Medical Sciences, Jodhpur, Rajasthan, India; Tanu Singhal, Department of Pediatrics, Kokilaben Dhirubhai Ambani Hospital and Medical Research Institute, Mumbai, India; Mangla Sood, Department of Pediatrics, IGMC, Shimla, Himachal Pradesh, India; Samsani Veena Sudeepthi, Department of Pediatrics, All India Institute of Medical Sciences, Raipur, India; Lokesh Tiwari, Department of Pediatrics, All India Institute of Medical Sciences, Patna, Bihar, India; Nishant Verma, Department of Pediatrics, King George's Medical University, Lucknow, Uttar Pradesh, India; Ruth Yonzon, Department of Pediatrics, New STNMMS Hospital, Gangtok, Sikkim, India.

Authors' Contributions NKB and RL contributed to the development and design of the study protocol, reviewed the literature, collated and analyzed the data, and wrote the first draft; MK and RMP were the formal data analysts for the study; SKK led the work of the study team; MIS-C study group did data collation, contributed to the study design; all co-authors critically reviewed the paper and approved the submitted version. The corresponding author attests that all listed authors meet authorship criteria. SKK will act as the guarantor for this paper.

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Data Availability On reasonable request.

Declarations

Conflict of Interest None.

References

1. Centers for Disease Control and Prevention. Emergency preparedness and response: Multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19). Health advisory. Available at: https://emergency.cdc.gov/han/2020/han00432.asp. Accessed on 22 May 2021.
2. Royal College of Paediatrics and Child Health. Guidance: paediatric multisystem inflammatory syndrome temporally associated with COVID-19. Available at: https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf. Accessed on 22 May 2021.
3. World Health Organization. Multisystem inflammatory syndrome in children and adolescents with COVID-19- Scientific Brief. Available at: https://apps.who.int/iris/rest/bitstreams/1277962/retrieve. Accessed on 22 May 2021.
4. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet. 2020;395:1771–8.
5. Abrams JY, Oster ME, Godfred-Cato SE, et al. Factors linked to severe outcomes in multisystem inflammatory syndrome in children (MIS-C) in the USA: a retrospective surveillance study. Lancet Child Adolesc Health. 2021;5:323–31.
6. Jain S, Sen S, Lakshmivenkateshiah S, et al. Multisystem inflammatory syndrome in children with covid-19 in Mumbai, India. Indian Pediatr. 2020;57:1015–9.

7. Henderson LA, Canna SW, Friedman KG, et al. American college of rheumatology clinical guidance for multisystem inflammatory syndrome in children associated with SARS-CoV-2 and hyperinflammation in pediatric COVID-19: Version 1. Arthritis Rheumatol. 2020;72:1791–805.
8. Ouldali N, Toubiana J, Antona D, et al. Association of intravenous immunoglobulins plus methylprednisolone vs immunoglobulins alone with course of fever in multisystem inflammatory syndrome in children. JAMA. 2021;325:855–64.
9. Son MBF, Murray N, Friedman K, et al. Multisystem inflammatory syndrome in children — initial therapy and outcomes. N Engl J Med. 2021;385:23–34.
10. McArdle AJ, Vito O, Patel H, et al. Treatment of multisystem inflammatory syndrome in children. N Engl J Med. 2021;385:11–22.
11. McCrindle BW, Li JS, Minich LL, et al. Coronary artery involvement in children with kawasaki disease: risk factors from analysis of serial normalized measurements. Circulation. 2007;116:174–9.
12. Maheshwari A, Mahto D, Kumar V, et al. Comparison of clinical and laboratory profile of survivors and non-survivors of SARS-CoV-2 related multisystem inflammatory syndrome of childhood in India: an observational study. J Paediatr Child Health. 2022;58:136–40.
13. World Health Organization. Living guidance for clinical management of COVID-19. WHO. Available at: https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-clinical-2021-2. Accessed on 2 Mar 2022.

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Atypical Kawasaki disease: Diagnosis underneath diapers

SK Tripathy, B Aggarwal, A Mandal, and NK Bagri

Department of Pediatrics, All India Institute of Medical Sciences (AIIMS), New Delhi, India
Address for correspondence: Dr. Bagri NK, E-mail: drnarendrabagri@yahoo.co.in

We report a 5-month-old baby, who presented with fever, irritability with rash for a total duration of 10 days, cough, and loose motions for 2 days. He was being treated as sepsis with broad-spectrum antibiotics before being referred to us. There were no history of erythema of tongue, conjuctival congestion, breathing difficulty, altered sensorium, or convulsion. Past history and perinatal history were unremarkable. On admission, the patient was febrile, irritable, and vitals were stable. Anthropometric measures including weight (=6 kg) and length (=63cm) of the baby were within normal range as per WHO standards. General physical examination revealed presence of urticarial rash, unilateral cervical lymphadenopathy, and edema of hands and feet but there were no oral or eye changes nor any periungal desqamation. On further examination and unfolding the diapers, we noted scrotal edema with perineal maculopapular rash which led us to consider Kawasaki disease (KD) as a possibility [Figure 1]. Laboratory evaluation revealed raised erythrocyte sedimentation rate (ESR) and C-reactive protein (50 mm/1st h and 34 mg/dL, respectively), anemia (Hb 5.8 g/dL), neutrophilic leukocytosis (20,200/mm^3), and thrombocytosis (platelet count: 6,00,000/mm^3). Ultrasonography of scrotum was suggestive of bilateral hydrocele. Echocardiography did not show any abnormalities consistent with KD. As our case did not met all the criteria for KD, a label of incomplete (or atypical) KD was considered as per American Heart Association (AHA) guidelines[1] and patient was started with intravenous immunoglobulin (IVIG) (2 g/kg over 12 h) and aspirin (75 mg/kg/day) on day 1 of hospitalization. After 24 h of IVIG therapy, the patient became afebrile, irritability reduced, and scrotal edema resolved in 48 h [Figure 2]. Repeat inflammatory markers (ESR, CRP, leucocyte count) were normal after 72 h although thrombocytosis (500,000/mm^3) continued. Blood culture was sterile. The patient was discharged on antithrombotic doses of aspirin. At 2 months follow-up, the child is doing fine and afebrile with normal echocardiography and inflammatory markers were normal.

KD is a self-limited vasculitis of unknown etiology often preceded by symptoms of upper respiratory or gastrointestinal illness like in our case.[2] Our patient had both upper respiratory infection and gastroenteritis at presentation. In the absence of classical features, these children often get misdiagnosed as sepsis and receive unwanted antibiotics without any benefit. The persistence of fever, presence of skin rash, edema of hands and feet and the scrotal edema pointed toward underlying vasculitis in our case.

Presence of scrotal swelling and pain due to testicular inflammation is characteristic of vasculitis including polyarteritis nodosa (PAN) (6%), Henoch-Schönlein Purpura (2%–38%) and KD.[3,4] Presence of rash especially over perineal area is seen in KD in initial few days of illness.[5] The appearance of scrotal edema in KD ranges from 4 to 18 days.[5] It is important for the physicians to know about this finding in KD to avoid unnecessary surgical exploration.

Diagnosis of KD remains a challenge, mainly when a child presents with incomplete or atypical features. A meticulous clinical examination can reveal clues such as scrotal edema and perineal rash to enable early diagnosis and timely initiation of therapy to prevent long-term complications.

Declaration of patient consent

The authors certify that appropriate patient consent was obtained.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, et al. Diagnosis, treatment and long term management of Kawasaki Disease: A Scientific Statement for Health Professionals from the American Heart Association. *Circulation.* 2017;135:927–99. [PubMed: 28356445]

2. Baker AL, Lu M, Minich LL, Atz AM, Klein GL, Korsin R, et al. Associated symptoms in the ten days before diagnosis of Kawasaki disease. *J Pediatr.* 2009;154:592–5. [PMCID: PMC2745188] [PubMed: 19038400]

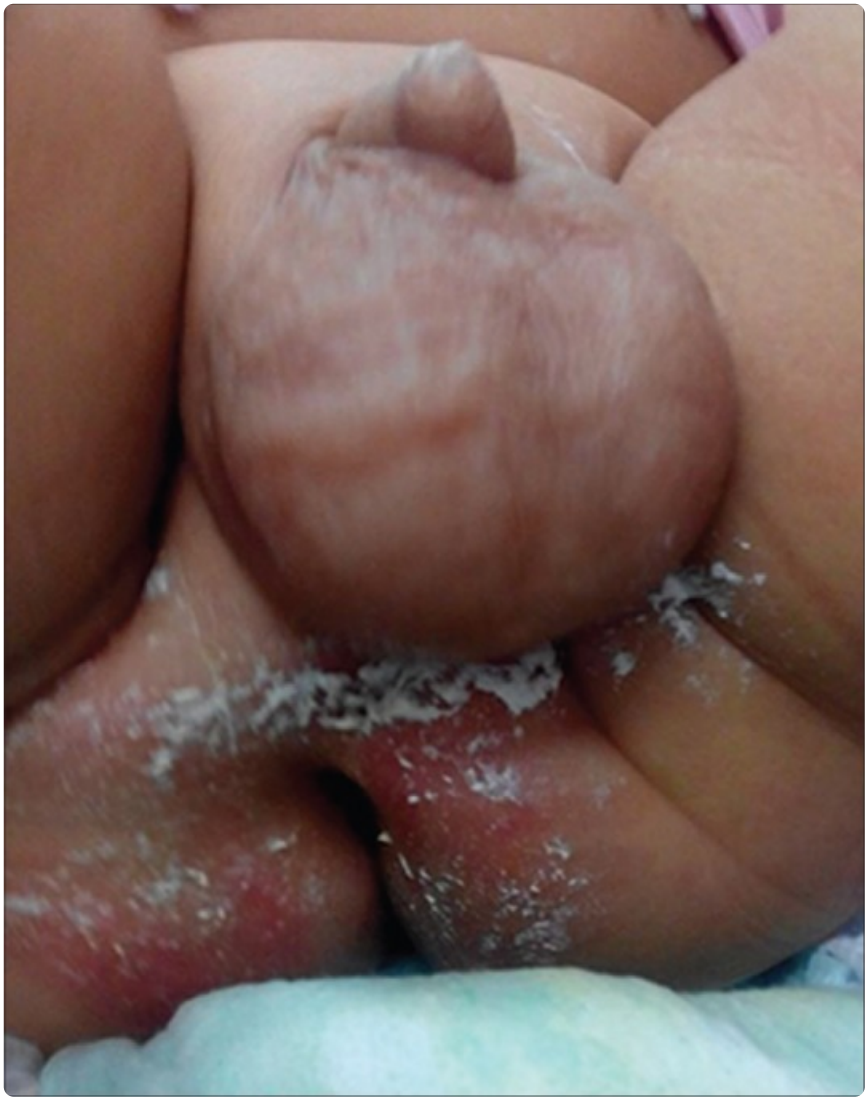
3. Eleftheriou D, Dillon MJ, Tullus K, Marks SD, Pilkington CA, Roebuck DJ, et al. Systemic polyarteritis nodosa in the young: A single centre experience over 32 years. *Arthritis Rheum.* 2013;65:2476–85. [PubMed: 23754739]

4. Ioannides AS, Turnock R. An audit of the management of the acute scrotum in children with Henoch-Schonlein Purpura. *J R Coll Surg Edinb.* 2001;46:98–9. [PubMed: 11329751]

5. Isidori C, Sebastiani L, Cardellini MC, Di Cara G, Rigante D, Esposito S. Early desquamating perineal erythema in a febrile infant: A characteristic clinical feature of Kawasaki disease. *Int J Environ Res Public Health.* 2017;14:710. [PMCID: PMC5551148] [PubMed: 28665334]

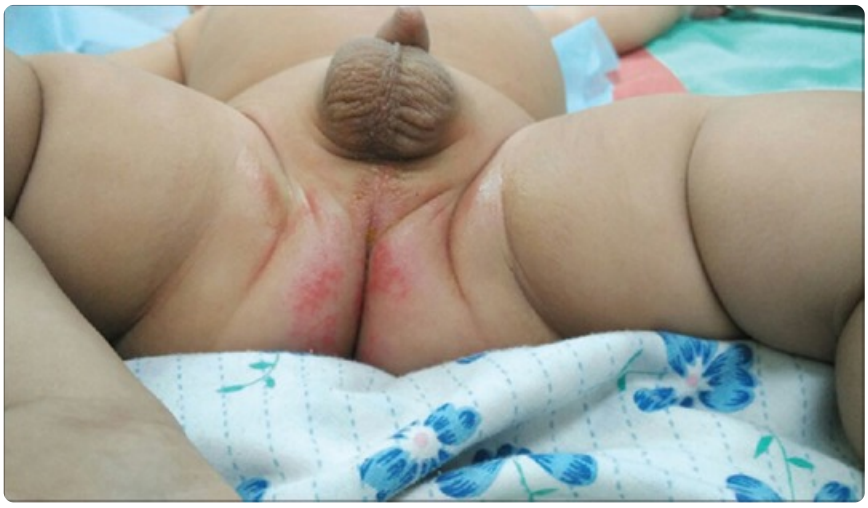
Figures and Tables

Figure 1



Presence of scrotal edema and perineal rash

Figure 2



Scrotal edema has resolved in 48 h after IVIG therapy

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CASE BASED REVIEW

Kawasaki disease or polyarteritis nodosa: coronary involvement, a diagnostic conundrum

Shivaprasad Pannasamudra Mohankumar[1] · Samannay Das[1] · P. Likitha[1] · Priyanka Naranje[2] · Manisha Jana[2] · Saurabh Kumar Gupta[3] · Narendra Kumar Bagri[4]

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Abstract

Polyarteritis nodosa (PAN) is a medium-vessel vasculitis presenting with cutaneous and multisystem involvement with considerable morbidity. The necrotizing vasculitis in PAN typically involves renal, celiac, and mesenteric vascular beds. Coronary artery involvement is a characteristic feature of Kawasaki disease, another medium-vessel vasculitis; however, it has been rarely reported with PAN. Here, we present 2 cases with PAN involving coronaries mimicking Kawasaki disease. A 3.5-year-old boy with classical features of Kawasaki disease with giant coronary aneurysm refractory to IVIg, methylprednisolone, infliximab presented with persistent rise in inflammatory markers and gastrointestinal bleeding. Digital subtraction angiography (DSA) revealed celiac artery branches stenosis and beading suggestive of PAN. Another 2-year-old girl presented with persistent fever, abdominal pain, and distension. She had hypertension, hepatomegaly, and splenomegaly on examination. Echocardiography revealed multiple coronary aneurysms and DSA revealed numerous renal artery aneurysms. Coronary aneurysm although is a rare presentation of childhood PAN, and can mimic Kawasaki disease. Although both are medium-vessel vasculitis differentiation between these two entities is pivotal, as there are differences in treatment modalities, duration of immunomodulatory therapy, and the outcome. This manuscript describes the salient differences which can help differentiate PAN masquerading as Kawasaki disease at initial presentation.

Keywords PAN · Coronary aneurysm · Cyclophosphamide · Kawasaki disease

Introduction

Polyarteritis nodosa (PAN) is a systemic vasculitis chiefly affecting medium vessels. Coronary involvement in childhood PAN has rarely been reported. Unlike Kawasaki disease, the predilection for coronary involvement is rare in PAN. However, at times the distinction between two vasculitides may be challenging, particularly at the onset, which has a bearing on the therapeutic plan and long-term outcome.

Shivaprasad Pannasamudra Mohankumar and Samannay Das are joint first authors.

✉ Narendra Kumar Bagri
drnarendrabagri@yahoo.co.in

Shivaprasad Pannasamudra Mohankumar
pmshivaprasad60@gmail.com

Samannay Das
rimon100393@gmail.com

P. Likitha
likhu13@gmail.com

Priyanka Naranje
priyanka11sh@gmail.com

Manisha Jana
manishajana@gmail.com

Saurabh Kumar Gupta
drsaurabhmd@gmail.com

[1] Department of Paediatrics, AIIMS, New Delhi, India

[2] Department of Radiodiagnosis and Interventional Radiology, AIIMS, New Delhi, India

[3] Department of Cardiology, AIIMS, New Delhi, India

[4] Division of Pediatric Rheumatology and Immunology, Department of Paediatrics, AIIMS, New Delhi, India

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Case report

Case 1 A three and half-year-old boy had a history of fever for 1 month, maculopapular rash over the trunk, periungual peeling, non-exudative conjunctivitis, and cheilitis. The child was diagnosed with Kawasaki disease and managed with oral steroids and low-dose aspirin for around a week with a transient resolution of symptoms. After 15 days, the child presented with chest pain, abdominal pain, fever, similar rash, and non-exudative conjunctivitis. The ECG was suggestive of inferior wall ischemia (Q wave in the lead 2, 3, and aVF). 2D echocardiography showed giant coronary aneurysms/dilations with the left main coronary artery (LMCA), left circumflex artery (LCx), and left anterior descending (LAD) measuring 7.1 mm (13 z score), 5.6 mm (11 z score), and 2.9 mm (2.5 z score), respectively, and right coronary artery (RCA) 2.7 mm (2.4 z score). The left ventricular ejection fraction (LVEF) was 45–50%. Inflammatory markers (CRP 187 mg/L and ESR 35 mmHg) were elevated. Kawasaki disease was diagnosed, and the child was treated with IVIg 2 g/kg, low-dose aspirin and low-molecular weight heparin (LMWH). The child continued to have fever and raised inflammatory markers (CRP 239 mg/L; ESR 48) with deteriorating cardiac function (EF 25–30%). The child was started on steroids, decongestive measures, and transiently required dobutamine support with the resolution of symptoms. He was discharged on oral steroids with tapering, oral enalapril, aspirin, and warfarin with a targeted INR of 2–3. After two months of asymptomatic period, the child presented with fever, blood in stools with persistently elevated inflammatory markers (CRP 170 mg/l and ESR 55), and echocardiogram showing increased coronary sizes (LMCA 15 z and LCx 12 z with dilated LAD 2.5 z and RCA 2.4 z). The child was treated with IV methylprednisolone 30 mg/kg in three pulses with symptom resolution. But the child had persistently elevated inflammatory markers with increasing coronary sizes, and hence a single dose of infliximab was also administered. Following this, a decline in CRP (CRP 2.3 mg/l) was observed, and he was discharged on tapering steroids, aspirin, warfarin, along with enalapril, and spironolactone. However, on tapering steroids, there was a resurgence in the levels of CRP. With GI bleed in the background with persistent increased coronary sizes and inflammatory markers, digital subtraction angiography (DSA) was performed, which showed stenosis and beading in branches of celiac arteries (Fig. 3a). Considering a long disease course of months with the elevation of inflammatory markers on weaning steroids and the characteristic DSA findings, the diagnosis was revised to PAN with the giant coronary aneurysm. The child was treated with cyclophosphamide pulse with a plan of six each monthly pulse followed by mycophenolate mofetil (MMF). The child has completed four cycles of cyclophosphamide and is doing well without recurrence of symptoms and normal inflammatory markers. Repeat echocardiography shows a decrease in the dimensions of the coronary arteries.

Case 2 A two-year-old girl presented with fever and abdominal pain for three months. The child had received multiple antibiotics for a presumed infection without any response. Echocardiography done as a part of the workup for persistent fever revealed multiple coronary artery aneurysms following which a diagnosis of Kawasaki disease was offered, and she received intravenous immunoglobulin (IVIG). However, because of persistent fever, she was referred to our center. Physical examination revealed pallor, stage I hypertension and hepato-splenomegaly (liver span of 9 cm with spleen palpable 3 cm below left costal margin). The rest of the systemic examination was unremarkable.

Investigations revealed anemia (Hemoglobin of 7 gm/dl), neutrophilic leukocytosis (total leucocyte count of TLC 26,000/mm^3 with neutrophil 80%), thrombocytosis (platelet count 6.6 lakh/mm^3) and raised inflammatory markers (CRP 30 mg/dl and ESR 40 mm 1st hour). The echocardiography revealed multiple coronary aneurysms (Figs. 1, 2).

In view of persistent fever, abdominal pain, and hypertension, the possibility of polyarteritis nodosa was considered, which was supported by DSA, which revealed multiple aneurysms in bilateral renal arteries (Fig. 3b). Contrast-enhanced computed tomography (CT) of the abdomen revealed multiple vasculitic infarcts involving bilateral kidneys and spleen.

She was managed with three doses of methylprednisolone 30 mg/kg/day followed by oral steroids and monthly intravenous cyclophosphamide at 500 mg/m^2 planned for

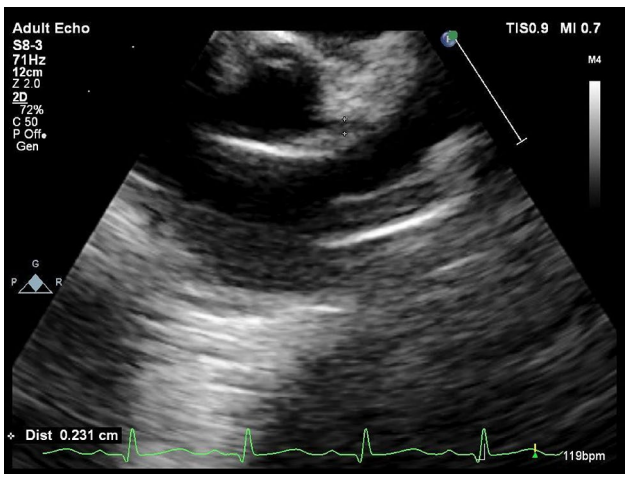

Fig. 1 ECHO showing dilatation of left anterior descending artery. RCA: 4 mm (+7.5 Z score) LMCA: 3.2 mm (+2.9 Z score) LAD: 2.9 mm (+5.2 Z score) EF: 60%

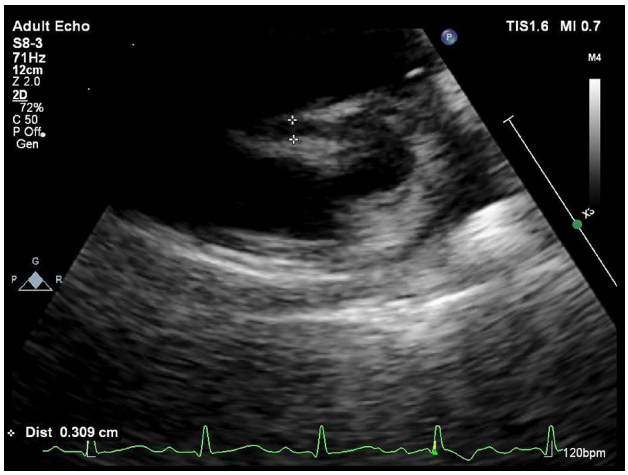

Fig. 2 ECHO showing dilatation of right coronary artery. RCA: 4 mm (+7.5 Z score) LMCA: 3.2 mm (+2.9 Z score) LAD: 2.9 mm (+5.2 Z score) EF: 60%

six months. Hypertension was managed with amlodipine and enalapril. The child has completed six cycles of cyclophosphamide and is doing well with no recurrence of symptoms. Currently, child is on oral MMF. Steroids were tapered and stopped. Repeat echocardiography shows a decrease in the dimensions of the coronary arteries.

Search strategy

We searched PubMed/Medline and Google scholar for articles with key words "Kawasaki versus Polyarteritis Nodosa", "Coronary involvement Polyarteritis Nodosa/ PAN", "Coronary involvement rheumatological diseases in children" the articles were carefully reviewed by first authors. We excluded articles in language other than English, irrelevant articles, and duplicates. Relevant articles to the topic of our discussion are included in literature review.

Discussion

These cases illustrate a rare clinical manifestation of childhood PAN in the form of coronary aneurysm, which is more frequently associated with Kawasaki disease (KD), leading to a diagnostic and therapeutic dilemma. Although both PAN and Kawasaki are medium-vessel vasculitis, usually with distinct clinical presentation, rarely can PAN have KD-like features as in our case 1.

Kawasaki disease, predominating in the toddler age group, presents with mucocutaneous rash and fever of acute onset along with or without coronary aneurysm [1, 2]. In contrast, the spectrum of organ involvement in PAN is wider, with a chronic course predominantly affecting school-age children and more widespread multisystem involvement in the form of hypertension, neuropathy, purpura or gangrene of skin, retinal vasculitis, aneurysm, and infarct in various sites like liver, spleen, gastrointestinal tract, and kidney [3–5].

The presence of coronary aneurysm is an atypical finding in PAN which, though rare, has been described in the literature. Histopathology performed post-mortem in adults with polyarteritis nodosa has demonstrated evidence of cardiac involvement with coronary arteritis found in 18/36 cases of necrotizing vasculitis on autopsy [6]. However, only a few reports of childhood PAN with coronary involvement exist. Our case 2 had a chronic course with fever and abdominal

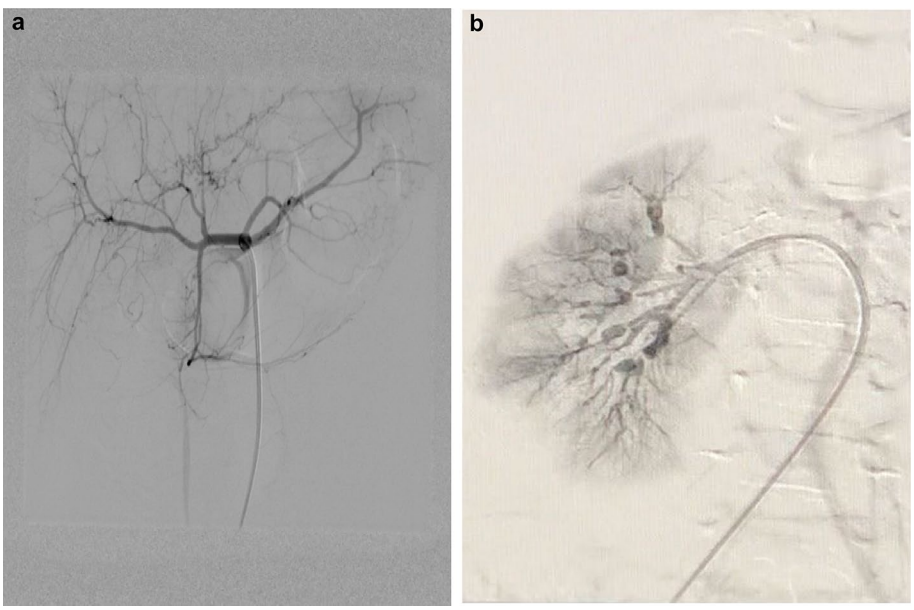

Fig. 3 **a** DSA showing stenosis and beading in celiac trunk branches; **b** DSA image showing aneurysm in the segmental renal arteries

pain for three months with hepato-splenomegaly, hypertension, and showed wedge-shaped infarcts in the kidney and spleen. The child met the EULAR/PRINTO/PRES 2010 classification criteria of childhood PAN established by [7]. Bowyer and coworkers presented two such cases in 1994 where the children had aneurysms in the coronary as well as in hepatic or renal vessels [8]. Munro and coworkers recently described a 3-month-old boy who had bloody diarrhea, fever, vomiting, a very high C-reactive protein, leukocytosis, and thrombocytosis [9], in whom, on autopsy, a generalized pan arteritis was revealed, including the coronary, renal, and mesenteric arteries, consistent with diagnosis of PAN. Canares and coworkers presented a case of a 16-year-old girl with PAN and coronary aneurysm who was successfully treated with pulse cyclophosphamide therapy [10]. Yamazaki-nakashimada and coworkers [11] reported a 3-year-old child with coronary involvement and rash. The child was initially suspected of having atypical Kawasaki and was refractory to IVIG. Child had finally improved with pulse methylprednisolone after diagnosis was revised to be childhood PAN due to multiple intra-abdominal visceral vascular involvement. Table 1 summarizes the reported cases of PAN with coronary involvement, including ours.

Both PAN and Kawasaki disease can present with a febrile illness, and it is challenging to differentiate between the two entities, particularly in the absence of typical dermatological features. Such a presentation may pose a diagnostic and therapeutic dilemma as the treatment option differs. Kawasaki disease presents more acutely with predominant affection to coronary vasculature, while PAN presents as a more insidious disease with multisystem involvement, vascular ulcer, and aneurysms in the celiac, mesenteric axis, and renal arteries (Supplementary Fig. 4) [12, 13]. Delineating the two conditions is essential to optimize the therapeutic strategy; IVIG is the first treatment option for Kawasaki disease. While prolonged immunosuppression withcyclophosphamide/MMF with steroids in this type of disease presentation having features of both diseases as indicated in PAN [10, 14]. Table 2 summarizes the key clinical and laboratory differences which can help to manage such challenging cases.

Kawasaki disease is an overt immunological reaction to superantigens mediated by T cells leading to infiltrates and inflammatory cascade. In contrast, in PAN, there is a pre-existing genetic predisposition or parainfectious activation of CD 8 + T cells with macrophages leading to the destruction of the vessel wall [15, 16].

In both cases, initial immunomodulation was as per the recent guidelines for the management of Kawasaki disease. However, the initial management with IVIG might have been insufficient for the underlying PAN, and the unchecked inflammation might have resulted in giant coronary aneurysms in both cases. This proves the value of the early diagnosis of PAN, even in cases of the coronary aneurysm,

Table 2 Comparing features of PAN and Kawasaki disease

	Kawasaki disease	Polyarteritis nodosa
Age	< 5 years usually	> 5 years
Fever	Acute onset	Insidious onset
Coronary involvement	Common	Rare
Skin manifestations	Maculopapular rash/edema/periungual peeling	Purpura, livedo reticularis, gangrene
Multisystem involvement	Rare	Common
· GI involvement	Rare	Common
· Renal involvement	Rare	Frequent
· Hypertension	Rare	Frequent
· ANCA positivity	Rare	Occasional
Disease course	Short (weeks)	Chronic
Therapy	Short (weeks)	Long (years)

Table 1 Reported cases of PAN with coronary involvement including our case

Author	Age/gender	Presentation	Coronary involvement	Other organs involved
Therese L Canares et al. (Paediatric rheumatology online journal)	16 Y/F	Fever and Arthritis	Yes (2 giant coronary aneurysms)	uveitis
Yamazaki-Nakashimada et al. (Seminars in arthritis and rheumatism)	3Y/F	Fever, pain abdomen, hypertension, neuropathy	Yes (Dilated right coronary artery 3.5 mm)	Intestinal perforation, pancreatitis
Bowyer et al. (The journal of rheumatology)	3Y/F	Fever, hypertension, seizure	Yes	Renal and hepatic aneurysms
Bowyer et al. (The journal of rheumatology)	15Y/F	Fever, rash, strawberry tongue	Yes	Renal aneurysm and Liver infarct
Munro et al. (Journal of paediatrics and child health)	3 M/M	Fever, hematochezia	Yes	Renal infarct and mesenteric vasculitis
Index case	2 Y/ F	Fever, abdominal distension	Yes	Renal infarct

without being biased towards a diagnosis of Kawasaki disease as coronary aneurysm is not a sine qua non for Kawasaki disease, particularly in cases with an unusually long course and persistently raised inflammatory markers like the index cases.

Conclusion

Coronary aneurysm, although a rare presentation of childhood PAN, can be a sole presenting feature and can mimic Kawasaki disease. However, prolonged course and persistently raised inflammatory markers can guide subsequent investigations like DSA for confirmatory diagnosis of PAN in such cases.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00296-023-05388-1.

Author contributions SPM, SD: literature review and wrote initial draft. LP, MJ, PN, SG: reviewed the draft. NB: concept, design, and review of the draft. All authors approved the final version of the draft. All authors take full responsibility for the integrity, accuracy, and all aspects of the work.

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Code availability Not applicable.

Declarations

Conflict of interest No conflict of interest among the authors.

Informed consent Informed consent was obtained from the patients' parents.

References

1. Zhu F, Ang JY (2021) 2021 update on the clinical management and diagnosis of Kawasaki disease. Curr Infect Dis Rep 23(3):3. https://doi.org/10.1007/s11908-021-00746-1
2. McCrindle BW, Rowley AH, Newburger JW, Burns JC, Bolger AF, Gewitz M, Baker AL, Jackson MA, Takahashi M, Shah PB, Kobayashi T, Wu MH, Saji TT, Pahl E, American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; Council on Cardiovascular Surgery and Anesthesia; and Council on Epidemiology and Prevention (2017) Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. Circulation 135(17):927–999. https://doi.org/10.1161/CIR.0000000000000484
3. Eleftheriou D, Dillon MJ, Tullus K, Marks SD, Pilkington CA, Roebuck DJ, Klein NJ, Brogan PA (2013) Systemic polyarteritis nodosa in the young: a single-center experience over thirty-two years. Arthritis Rheum 65(9):2476–2485. https://doi.org/10.1002/art.38024
4. Kawakami T (2012) A review of pediatric vasculitis with a focus on juvenile polyarteritis nodosa. Am J Clin Dermatol 13(6):389–398. https://doi.org/10.2165/11599660-000000000-00000
5. Forbess L, Bannykh S (2015) Polyarteritis nodosa. Rheum Dis Clin North Am 41(1):33–46. https://doi.org/10.1016/j.rdc.2014.09.005. (**vii**)
6. Schrader ML, Hochman JS, Bulkley BH (1985) The heart in polyarteritis nodosa: a clinicopathologic study. Am Heart J 109:1353–1359. https://doi.org/10.1016/0002-8703(85)90365-5
7. Ozen S, Paediatric Rheumatology International Trials Organisation (PRINTO) et al (2010) EULAR/PRINTO/PRES criteria for Henoch-Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008. Part II: Final classification criteria. Ann Rheum Dis 69(5):798–806. https://doi.org/10.1136/ard.2009.116657
8. Bowyer S, Mason WH, McCurdy DK, Takahashi M (1994) Polyarteritis nodosa with coronary aneurysms: the Kawasaki-PAN controversy revisited (letter). J Rheumatol 21:1585
9. Munro AR, Beasley SW, Pattemore PK, Fraser R (2003) Fatal late onset necrotising enterocolitis in a term infant: atypical Kawasaki disease or polyarteritis nodosa of infancy? J Paediatr Child Health 39:555–557. https://doi.org/10.1046/j.1440-1754.2003.00217.x
10. Canares TL, Wahezi DM, Farooqi KM, Pass RH, Ilowite NT (2012) Giant coronary artery aneurysms in juvenile polyarteritis nodosa: a case report. Pediatr Rheumatol 10:1–5. https://doi.org/10.1186/1546-0096-10-1
11. Yamazaki-Nakashimada MA, Espinosa-Lopez M, Hernandez-Bautista V, Espinosa-Padilla S, Espinosa-Rosales F (2006) Catastrophic Kawasaki disease or juvenile Polyarteritis nodosa? Semin Arthritis Rheum 35(6):349–354. https://doi.org/10.1016/j.semarthrit.2006.02.002
12. Jennette J (2003) The relationship of Kawasaki disease to other systemic vasculitides. Pediatr Res 53:158. https://doi.org/10.1203/00006450-200301000-00028
13. Khanna S, Garikapati K, Goh DSL et al (2021) Coronary artery vasculitis: a review of current literature. BMC Cardiovasc Disord 21:7. https://doi.org/10.1186/s12872-020-01813-6
14. Cohen RD, Conn DL, Ilstrup DM (1980) Clinical features, prognosis, and response to treatment in polyarteritis. Mayo Clin Proc 55(3):146–155
15. Takahashi K, Oharaseki T, Yokouchi Y (2014) Update on etio and immunopathogenesis of Kawasaki disease. Curr Opin Rheumatol 26(1):31–36. https://doi.org/10.1097/BOR.0000000000000010
16. Parada-Turska J, Turska M (2018) The changing face of medium-sized vasculitis. Wiad Lek 71(1 pt 1):64–72

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EDITORIAL COMMENTARY

The Enigma of Pediatric Multisystem Inflammatory Syndrome Temporally Associated with SARS-CoV-2 (PMIS-TS)

Narendra Kumar Bagri[1]

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The clinical syndrome of pediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 (PMIS-TS) or multisystem inflammatory syndrome in children (MIS-C) was first reported during April–May 2020 [1–3]. Since then, though the literature describing the clinical spectrum has expanded, the exact pathogenesis still remains elusive and there is lack of high-level evidence to guide the most appropriate therapeutic regimen for PMIS-TS.

In this issue of Indian Journal of Pediatrics, Elilarasi et al. have published a series of 65 children with PMIS-TS from southern India [4]. This study elucidates the clinical spectrum of PMIS-TS. Despite similarities with other global and Indian series, there are certain peculiarities in this paper, such as higher frequency of coronary involvement; 67% of the study group had coronary dilatation. This is in contrast to other series from northern India reporting coronary involvement in 19%–20% of the study subjects [5, 6]. In our experience most of these resolved at 6-wk follow-up [5]; however, the outcome of coronary abnormalities has not been reported in the present study. In the Elilarasi et al. study, 75% (3/4) of children presenting with acute abdomen were operated [4]; this is an alarming observation and re-emphasizes the fact that PMIS-TS can present with various gastrointestinal manifestations including acute abdomen; and a high index of suspicion can avoid unwarranted surgical interventions. Another intriguing observation in this series is the presence hypertension observed in one child, although the authors have not discussed the possible reasons for same, it might not be related to PMIS-TS, which typically presents with hypotension.

The study team has made all possible attempts to rule out coinfections such as dengue, scrub typhus, etc., which is very crucial in settings like India, as there would be many infectious febrile conditions, which may have clinical features overlapping with PMIS-TS. With increasing seroprevalence for COVID antibodies, many febrile illnesses shall meet the definition of PMIS-TS. If overlooked, these children with underlying alternative diagnosis may erroneously receive immunosuppressive agents, particularly steroids, which may flare up the underlying infection.

Thus, till a reliable diagnostic biomarker of PMIS-TS is available or the existing definitions are revised, the onus lies on us clinicians to exclude all possible causes of fever before committing the diagnosis of PMIS-TS. On the other hand, timely diagnosis of PMIS-TS is also equally important to curtail the morbidity and mortality associated with PMIS-TS. The reported mortality in Indian series including the present study is high (6%–27%) as compared to the western world (1%–2%) [5–7]; these observations highlight the need of opportune diagnosis and management of PMIS-TS.

Declarations

Conflict of Interest None.

References

1. World Health Organization. (2020). Multisystem inflammatory syndrome in children and adolescents with COVID-19: scientific brief, 15 May 2020. World Health Organization. Available at: https://apps.who.int/iris/handle/10665/332095. Accessed on 22 May 2020.
2. Royal College of Paediatrics and Child Health. Guidance: paediatric multisystem inflammatory syndrome temporally associated with COVID-19. Available at: https://www.rcpch.ac.uk/resources/guidance-paediatric-multisystem-inflammatory-syndrome-temporally-associated- covid-19. Accessed on 22 May 2020.
3. Centers for Disease Control and Prevention. Emergency preparedness and response: multisystem inflammatory syndrome

✉ Narendra Kumar Bagri
drnarendrabagri@yahoo.co.in

[1] Division of Pediatric Rheumatology, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi 110029, India

in children (MIS-C) associated with coronavirus disease 2019 (COVID-19). Health advisory. Available at: https://emergency.cdc.gov/han/2020/han00432.asp. Accessed on 6 July 2022.
4. Elilarasi S, Poovazhagi V, Kumaravel G, Srividya VG, Solomon JRS. Pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. Indian J Pediatr. 2021:1–6. https://doi.org/10.1007/s12098-021-03954-8.
5. Bagri NK, Deepak RK, Meena S, et al. Outcomes of multisystem inflammatory syndrome in children temporally related to COVID-19: a longitudinal study. Rheumatol Int. 2022;42:477–84.
6. Maheshwari A, Mahto D, Kumar V, et al. Comparison of clinical and laboratory profile of survivors and non-survivors of SARS-CoV-2-related multisystem inflammatory syndrome of childhood in India: an observational study. J Paediatr Child Health. 2022;58:136–40.
7. Son MBF, Murray N, Friedman K, et al; Overcoming COVID-19 Investigators. Multisystem inflammatory syndrome in children-initial therapy and outcomes. N Engl J Med. 2021;385:23–34.

Methylprednisolone or Intravenous Immunoglobulin in Children with Paediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2 (PIMS-TS)?

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SUMMARY

Welzel, et al. [1] recently published a randomized controlled trial (RCT) comparing the efficacy of methylprednisolone (MP) with intravenous immunoglobulin (IVIg) for COVID-19 associated pediatric inflammatory multisystem syndrome, also referred to as COVID-19 associated multisystem inflammatory syndrome in children (MIS-C). This study was necessitated by the helplessness associated with the condition, in the face of the COVID pandemic, coupled with the ray of hope offered by these medications, documented through physician experiences and observational studies.

Table I summarizes the salient features of the RCT, and **Box I** presents the main results.

COMMENTARIES

Evidence-based Medicine Viewpoint

Critical Appraisal

The methodological aspects of the RCT conformed to the criteria for low to moderate risk of bias. Random sequence generation, and allocation concealment appeared to be adequate. However, there was no blinding of the outcome assessors and treating physicians. This could directly or indirectly impact the reporting of several outcomes studied in this RCT. Thankfully, there was no attrition or selective outcome reporting. The trial was described as investigator-initiated, hence it is presumed that pharmaceutical companies producing/marketing the study medications had no role in the design, conduct, or analysis stages of the trial.

As expected in a well-designed RCT, there were several methodological refinements. As far as practically feasible, the investigators used clearly defined criteria for situations that are often loosely reported. Thus, there were clearly specified criteria for the condition being studied viz. COVID-19 associated Pediatric Inflammatory Multisystem Syndrome (PIMS). There were also clear definitions for terms such as organ support, PIMS phenotype, cardiac dysfunction, each of the serious adverse events studied, and criteria for defining the duration of the primary outcome. This diminished the subjectivity that could creep in when outcomes were recorded by unblinded observers.

The choice of the primary outcome was rational, considering that duration of hospitalization is a fairly objective parameter, is patient-centric in character, and also considers the need(s) of the healthcare system in general. Surrogate outcomes reflecting the body's response to widespread inflammation (viz. absolute and relative levels of biomarkers, and their changes over time) may be convenient to record, but are less relevant than objective patient-centric outcomes.

The investigators employed robust statistical methods for data analysis. Several subgroup analysis and sensitivity analyses were undertaken to test the robustness of the results. As expected, the trial was properly registered, and the protocol published.

However, there are some issues that merit closer attention. The definition for COVID-associated PIMS was based on the temporal association with microbiologically confirmed SARS-CoV-2 infection or 'putative' contact. However, the definition and implication of the word 'putative' are somewhat unclear. Ordinarily this would not have been important; however in this RCT, the number of children with microbiologically confirmed COVID was not reported. Further, almost two-thirds of the enrolled children had known exposure to COVID, while one-third were previously PCR positive. The duration of 'previous' was also not specified.

The sample size calculation was based on an anticipated effect size of 2.5 days' difference between the duration of hospitalization in the two groups. However, it is unclear on what basis this difference was anticipated; and also whether the investigators *a priori* expected the intervention (methylprednisolone) to be superior, inferior, or equivalent to

Table I Summary of the Trial

PICOTS elements	*Population/Problem*: Children with COVID-19 associated pediatric inflammatory multisystem syndrome (PIMS) *Intervention*: Methylprednisolone (MP); Comparison: Intravenous immunoglobulin (IVIG) *Outcome(s)*: Duration of hospitalization, mortality, clinical parameters, need for supportive therapy. *Timeframe of outcome measurement*: Up to 28 d following hospital admission Setting: Hospital
Clinical question	In children admitted with COVID-19 associated PIMS, what is the efficacy of MP, compared to IVIG, on the duration of hospitalization and mortality within 28 d of admission?
Study design	Multi-centric, open-label, pragmatic randomized controlled trial.
Study setting	Ten hospitals located in Switzerland.
Study duration	Around one year for enrolment (21 May, 2021 – 15 April, 2022), with follow-up for 28 d after admission.
Inclusion criteria	Children (<18y), admitted with COVID-19 associated PIMS. The condition was defined as per the prevalent national and international (consensus) guidelines viz., the presence of fever, elevated inflammatory biomarkers, (one or more) organ dysfunction, confirmed COVID-19 (SARS-CoV-2) infection or contact with a case, after excluding other possible diagnoses.
Exclusion criteria	Undefined medical history deemed to endanger patients in case of study participation, contrain-dication(s) to either of the treatments, unspecified clinical indication necessitating that only one of the treatments could be administered, and newborns with corrected gestational age less than 44 weeks.
Recruitment procedure	Not specified.
Randomization	A computer program was used on an online platform to generate the allocation sequence in blocks of 30, without site-stratification. The allocation ratio was 1:1.
Allocation concealment	Although not described in detail, it appears to have been done by accessing the online platform for enrolment of individual participants.
Blinding	Participants, their families, treating physicians,, and outcome assessors were not blinded to the allocation. However, the statistician analyzing the data was blinded.
Execution of the Intervention (and Comparison)	MP was administered intravenously 10 mg/kg, once daily for three days (maximum dose capped at 1 g/d); IVIG was administered 2 g/kg single dose infused over 8-16 hours (dose capped at 100 g). The medications were administered through central or peripheral intravenous access. Additional treatment options such as fluids, anticoagulant medication, antibiotics, and organ supportive therapies/procedures could be administered at the discretion of the treating physicians. They could also administer additional anti-inflammatory medications based on clinical judgement, which included oral steroids, anakinra, and combinations of these. Treating physicians also had the freedom to use both study medications and switch medications, if they desired, and also to use greater or fewer doses of the allocated study medication.
Outcomes	The primary outcome was the duration of hospitalization (defined as the interval between hospital admission and discharge or death, within 28 d). Secondary outcomes were duration of hospitalization after randomization; all-cause mortality; requirement of organ support and the respective durations (viz., respiratory support categorised as invasive ventilation, non-invasive ventilation with either mode, or supplemental oxygen {high or low flow}, inotrope use, renal replacement therapy, or ECMO); abnormal cardiac evaluation (specifically coronary arterial dilatation, left ventricular ejection fraction <55%, or arrhythmia); and adverse events (major bleeding, thrombotic event, both, and other events that could be attributed to the study medications).
Follow-up protocol	None (outside the timeframe for capturing the primary outcome).
Sample size	The investigators calculated that recruiting 40 participants in each arm would be adequate to detect an effect size of 2.5 days difference in hospitalization between the trial arms, with α=5% and β=20%.
Data analysis	Intention-to-treat analysis was planned and executed, wherein those randomized were analyzed in the trial respective arms, regardless of what they actually received.
Comparison of groups baseline	The participants in the two trials arms appeared to have similar age distribution, gender ratio, body at weight, body mass index, and ethnicity. The baseline vital signs (heart rate, respiratory rate, oxygen saturation, and capillary refill time) were comparable. There were no apparent differences in the clinical features such as fever, cardiovascular instability features, gastrointestinal manifestations, mucocutaneous features, neurologic manifestations, or respiratory symptoms. Key laboratory parameters such as blood cell counts, CRP, D-dimer level, ferritin, troponin, and brain natriuretic peptide, also appeared comparable.

Box I Summary of the Main Results (Intervention vs Comparison)

Primary outcome

- Median (IQR) duration of hospitalization: 6.0 (4.0, 8.0) vs 6.0 (5.0, 8.8) d

Secondary outcomes

- Median (IQR) duration of hospitalization after randomization: 5.0 (4.0, 7.0) vs 5.5 (5.0, 8.0) d
- All-cause mortality: 0/37 vs 0/38
- Proportion requiring respiratory support (at any time): 10/37 vs 21/38 (P<0.05)
- Proportion requiring respiratory support (after randomization): 3/37 vs 11/38 (P<0.05)
- Median (IQR) duration of respiratory support: 2.5 (1.3, 4.8) vs 2.0 (1.0, 4.0) d
- Proportion requiring inotrope medication (at any time): 10/37 vs 15/38
- Median (IQR) duration of inotrope support: 2.0 (1.3, 3.0) vs 2.0 (1.5, 3.0) d
- Proportion requiring renal replacement therapy (at any time): 0/37 vs 0/38
- Proportion requiring ECMO (at any time): 0/37 vs 0/38
- Proportion with coronary arterial dilatation: 2/37 vs 4/38
- Proportion with left ventricular ejection fraction <55%: 5/37 vs 9/38
- Proportion with arrhythmia: 2/37 vs 1/38
- Proportion requiring ICU admission: 15/37 vs 20/38
- Proportion with pre-specified adverse events: 0/37 vs 1/38
- Proportion with adverse events possibly related to the study medications: 2/37 vs 1/38 (P<0.05)

IvIg. The distinctions are important because sample size calculations can vary.

Being a pragmatic RCT conducted during the peak of the COVID-19 pandemic, treating teams had the liberty to use non-study medications without clearly defining their reasons. Although they were advised to desist for at least 24 hours after randomization, the elegant Sankey diagram [1] suggests that this dictum was not strictly adhered to. Further, as many as 41 of the 75 participants (55%) received non study medications. In fact, two-thirds in the methylprednisolone arm received additional medications, about half of whom received IvIg as well. Similarly, among those allocated to receive IvIg, almost half received other medications, one-third of whom received methylprednisolone. Thus, 23 of 75 (31%) participants ultimately received both medications (though not always concomitantly). It would be valuable to study their data separately, since there is evidence suggesting that combined therapy with both medications may be associated with shorter hospitalization in intensive care units [2]. In this RCT [1], it is difficult to determine whether the comparability of the two arms was related to true therapeutic equivalence, or if was artefactual due to participants receiving non-study medications.

How to explain the apparent beneficial impact of methylprednisolone on the requirement for respiratory support? On the one hand, the need for support were lower in those receiving methylprednisolone. On the other hand, the duration of support was not significantly reduced. Although less than 15% children had respiratory distress and/or need for oxygen at baseline, this increased two to three fold during therapy. Further, although the investigators outlined the extent of 'respiratory support' that could be provided, the data on invasive ventilation, non-invasive ventilation, and supplemental oxygen were not shown. The investigators themselves suggested that baseline differences in the trial arms could (at least) partly explain their findings; however the data presented did not reflect such baseline differences. These observations suggest that the data on respiratory support need more careful evaluation before firm conclusions can be drawn.

The investigators highlighted that their Bayesian analysis showed moderate benefit of methylprednisolone over IvIg. This was based on 80% probability of a shorter hospitalization duration. However, careful examination of the data show that the credible interval of the difference in hospitalization duration,crossed the line of no effect (-2.3 days, 1.0 days) confirming a statistically insignificant result. Of course, ideally the investigators should have categorised the levels of benefit, taking into account the credible intervals. In short, moderate benefit should have been defined as an 80% probability that the credible interval would remain on either side of 0.

To be fair, the investigators did highlight some of the other limitations in their RCT [1]. These included narrowly missing the planned sample size, inadequate power to comment on secondary outcomes and/or subgroups, wide latitude to individual clinicians to deviate from the allocated medications, inability to analyse data of eligible but unrandomized children, absence of blinding, minor distinction between duration of hospitalization calculated from the time of admission, vs. time of randomization; and limiting the follow-up duration to 28 days. These self-declared limitations suggest that the investigators held a balanced approach to their findings. The investigators did not disclose the data of individual hospitals, which can be helpful if there are differences amongst trial sites.

The investigators extensively discussed current as well as anticipated studies addressing the research question, comparing and contrasting their data with other data. However, one aspect was not considered, which is the learning curve in physician behavior and responses during

the pandemic. At the onset, when treatment strategies were unclear, most physicians were cautious in prescribing novel medications, This gave way to liberalized prescriptions of (sometimes) multiple anti-inflammatory agents (evidenced by the frequent use of additional therapies in the enrolled participants), followed by a more tempered approach once the desperation associated with managing PIMS abated somewhat. The last phase with greater experience coincided with less lethal variants of the virus also. Therefore, it would be interesting and instructive to review the trial data during quarterly epochs of the study.

CONCLUSION

This well-designed RCT showed that treatment with methylprednisolone in children with COVID-associated PIMS, resulted in a similar duration of hospitalization, compared to those receiving IVIG alone. Barring the need for (unspecified) respiratory support which was less frequent in those randomized to receive methylprednisolone, other clinical and biomarkers of organ dysfunction were comparable between groups. However, the issues highlighted above, and the frequent use of combinations of both medications, necessitates additional data analysis and external validation, before the two medications can be considered equivalent.

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JOSEPH L MATHEW
Department of Pediatrics,
PGIMER, Chandigarh, India.
dr.joseph.l.mathew@gmail.com

REFERENCES

1. Welzel T, Atkinson A, Schöbi N, et al. Methylprednisolone versus intravenous immunoglobulins in children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS): an open-label, multi-centre, randomised trial. Lancet Child Adolesc Health. 2023; 7:238-48.
2. Harthan AA, Nadiger M, McGarvey JS, et al. Early combination therapy with immunoglobulin and steroids is associated with shorter ICU length of stay in multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19: A retrospective cohort analysis from 28 U.S. Hospitals. Pharmacotherapy. 2022;42:529-39.

Pediatric Rheumatologist's Viewpoint

The PIMS-TS shares many clinical features with Kawasaki disease. The use of intravenous immunoglobulin (IVIG) as the initial immunomodulatory agent stems from the recommendations for the management of Kawasaki disease [1]. Subsequently, many large observational studies with propensity score matching were conducted to study the best immuno-modulatory treatment for PIMS-TS using IVIG or steroids alone or in combination [2-4]. For pragmatic reasons, conducting a randomized controlled trial comparing the efficacy of IVIG vs steroids to identify the ideal therapeutic option has been a challenge during the ongoing pandemic.

The RCT by Welzel, et al. [5] gives meaningful insight regarding the choice of initial immunomodulatory agent in the management of PIMS-TS. The results of this RCT have shown a comparable efficacy (duration of hospital stay) of intravenous methylprednisolone (MP) and IVIG. Also, fewer subjects in the group receiving intravenous MP required respiratory support compared with those receiving IVIG. These findings are of relevance to LMICs (low middle-income countries) like ours where the approximate cost of treating a 30 kg child with PMIS-TS using IVIG (2 g/kg) would cost INR 1,00,800 vs INR 3600 for intravenous MP (10 mg/kg/day for 3 days). Apart from the approximate 28-fold cost benefit, the use of intravenous MP as a first-line treatment option for PMIS-TS would also help in combatting the shortage of IVIG during these highly demanding times. These results are in sync with the initial BATS (best available treatment study) group, which showed a comparable composite primary outcome (ionotropic support or mechanical ventilation by day 2 or later, or death) in children receiving either IVIG or glucocorticoids alone [3]. Though the present RCT did not permit the combination of IVIG plus glucocorticoids, a recent study from Channon-Wells, et al. [6] has suggested a marginal gain of combination therapy. Moreover, the coronary outcomes were also similar in all treatment arms (IVIG alone, steroids alone and IVIG plus steroids combination). Given the results of this RCT and the existing evidence, it seems that steroids may be used as a first-line option for the management of PIMS-TS in our settings. However, the author cautions against overdiagnosis of PMIS-TS, particularly amid increasing seropositivity for SARS-CoV-2 and the resultant unwarranted use of steroids.

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NARENDRA KUMAR BAGRI
Division of Pediatric Rheumatology,
Department of Pediatrics
AIIMS, New Delhi.
drnarendrabagri@yahoo.co.in

REFERENCES

1. Henderson LA, Canna SW, Friedman KG, et al. American College of Rheumatology Clinical Guidance for Multisystem Inflammatory Syndrome in Children Associated With SARS–CoV 2 and Hyperinflammation in Pediatric COVID 19: Version 1. Arthritis Rheumatol. 2020;72:1791–805.
2. Son MBF, Murray N, Friedman K, et al. Multisystem inflammatory syndrome in children – initial therapy and outcomes. N Engl J Med. 2021;12.
3. McArdle AJ, Vito O, Patel H, et al. Treatment of multisystem inflammatory syndrome in children. N Engl J Med. 2021;12.
4. Bagri NK, Khan M, Pandey RM, et al. Initial immunomodu-

lation and outcome of children with multisystem inflammatory syndrome related to COVID-19: a multisite study from India. Indian J Pediatr. 2022;89:1236-42.
5. Welzel T, Atkinson A, Schöbi N, et al. Methylprednisolone versus intravenous immunoglobulins in children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS): an open-label, multicentre, randomised trial. Lancet Child Adolesc Health. 2023; S2352464223000202.
6. Channon-Wells S, Vito O, McArdle AJ, et al. Immunoglobulin, glucocorticoid, or combination therapy for multisystem inflammatory syndrome in children: a propensity-weighted cohort study. Lancet Rheumatol. 2023; S2665991323 000292.

Pediatrician's Viewpoint

Since MIS-C, a new hyperinflammatory syndrome that emerged post-COVID-19, was first described there was a dilemma about its optimal management. Due to the overlapping clinical and laboratory features, management was extrapolated based on experiences in treating Kawasaki disease, toxic shock syndrome and macrophage activation syndrome. Anti-inflammatory treatment ranged from intravenous immunoglobulin (IVIG), methylprednisolone, combination of both, to biologics (anakinra, tocilizumab, TNF blockers).Though initially IVIG formed the mainstay of therapy, but with time the use of steroids, specially methylprednisolone, either as monotherapy or in combination with IVIG, significantly increased during the second wave. However, there was no head-to-head RCT showing superiority of one form over the other.

The current study is an open label, multi-center two arm RCT, where MIS-C patients requiring anti-inflammatory treatment were randomized to either IVIG or pulse methylprednisolone therapy. Primary outcome was the length of hospital stay, and secondary outcomes were need for organ support. It is important to note that this is the first publication where the two principal drugs for treating MIS-C are compared through RCT.

The study shows that the median length of hospital stay was similar in both the groups and the need for respiratory support was statistically lesser in the methylprednisolone group, without much variation in the need for inotropes, ICU admission, and cardiac events between the two groups. The authors conclude that intravenous methylprednisolone can be an acceptable first line treatment for MIS-C.

There are several limitations to the study, principal being the small sample size and non enrollment of a sizeable number of patients as it was perceived that they will require a combined therapy with IVIG and methylprednisolone. The data pertaining to the initial clinical characteristics between the enrolled and non-enrolled were not analyzed, thereby raising the possibility of a biased sampling. Furthermore, there is no data on the coronary involvement at follow-up between the two groups which has a bearing on the long-term prognosis.

The study is significant considering that it is a RCT whereby methylprednisolone was shown as non-inferior to IVIG, and being significantly cheaper and globally more readily available, would definitely be a more viable treatment option for middle income countries like ours.

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PRIYANKAR PAL
Department of Pediatrics
Institute of Child Health, Kolkata, West Bengal.
mailme.priyankar@gmail.com

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Rheumatology
INTERNATIONAL

OBSERVATIONAL RESEARCH

Outcomes of multisystem inflammatory syndrome in children temporally related to COVID-19: a longitudinal study

Narendra Kumar Bagri[1] · Rakesh Kumar Deepak[2] · Suneeta Meena[3] · Saurabh Kumar Gupta[4] · Satya Prakash[8] · Kritika Setlur[8] · Jagatshreya Satapathy[8] · Karan Chopra[8] · Ashish Datt Upadhyay[5] · Sivasubramanian Ramakrishnan[4] · Rakesh Lodha[8] · Lalit Dar[6] · Anjan Trikha[7] · Sushil Kumar Kabra[8]

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Abstract

To study the clinical, laboratory characteristics and outcomes of multisystem inflammatory syndrome in children (MIS-C) temporally related to coronavirus disease 2019 (COVID-19) in a resource-limited setting. All children meeting the World Health Organization case definition of MIS-C were prospectively enrolled. Baseline clinical and laboratory parameters were compared between survivors and non-survivors. Enrolled subjects were followed up for 4–6 weeks for evaluation of cardiac outcomes using echocardiography. The statistical data were analyzed using the stata-12 software. Thirty-one children with MIS-C were enrolled in an 11-month period. Twelve children had preexisting chronic systemic comorbidity. Fever was a universal finding; gastrointestinal and respiratory manifestations were noted in 70.9% and 64.3%, respectively, while 57.1% had a skin rash. Fifty-eight percent of children presented with shock, and 22.5% required mechanical ventilation. HSP like rash, gangrene and arthritis were uncommon clinical observations.The median duration of hospital stay was 9 (6.5–18.5) days: four children with preexisting comorbidities succumbed to the illness. The serum ferritin levels (ng/ml) [median (IQR)] were significantly higher in non-survivors as compared to survivors [1061 (581, 2750) vs 309.5 (140, 720.08), p value = 0.045]. Six patients had coronary artery involvement; five recovered during follow-up, while one was still admitted. Twenty-six children received immunomodulatory drugs, and five improved without immunomodulation. The choice of immunomodulation (steroids or intravenous immunoglobulin) did not affect the outcome. Most children with MIS-C present with acute hemodynamic and respiratory symptoms.The outcome is favorable in children without preexisting comorbidities.Raised ferritin level may be a poor prognostic marker. The coronary outcomes at follow-up were reassuring.

Keywords MIS-C · SARS-CoV-2 · Coronary artery outcomes · MIS-C and Kawasaki disease

✉ Narendra Kumar Bagri
drnarendrabagri@yahoo.co.in

1 Division of Pediatric Rheumatology, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India

2 Department of Transplant Immunology and Immunogenetics, All India Institute of Medical Sciences, New Delhi, India

3 Department of Laboratory Medicine, All India Institute of Medical Sciences, New Delhi, India

4 Department of Cardiology, All India Institute of Medical Sciences, New Delhi, India

5 Department of Biostatistics, All India Institute of Medical Sciences, New Delhi, India

6 Department of Microbiology, All India Institute of Medical Sciences, New Delhi, India

7 Department of Anesthesiology and Critical Care, All India Institute of Medical Sciences, New Delhi, India

8 All India Institute of Medical Sciences, New Delhi, India

Introduction

Multisystem inflammatory syndrome following COVID-19 infection from various pediatric clusters was first reported in January 2020 from Europe and North America [1–3]. Following these reports, the World Health Organization (WHO) circulated a preliminary case definition for multisystem inflammatory disorder temporally associated with COVID in children and adolescents (MIS-C) for reporting surveillance and outlining treatment strategies for this disorder [4]. This entity is also known as Multisystem inflammatory syndrome in children associated with COVID-19and Pediatric Multisystem inflammatory syndrome temporally associated with SARS-CoV-2(PIMS-TS) [5, 6].

The clinical spectrum of MIS-C includesmild persistent febrile illness, Kawasaki diseases like illness and severe MIS-C presenting with shock and multiorgan involvement [7]. The severe form of MIS-C is a life-threatening disease,

with a mortality of 2%, as reported from a large series of 518 children from the US [8]. Its resemblance to Kawasaki disease also poses a risk of cardiac and coronary involvement to children with MIS-C, with 8–24% of the cases developing coronary artery abnormalities [9]. However, there is a paucity of data on the outcome of MIS-C fromresource-poor settings. In contrast to the developed world, resource-poor settings arechallenged withfactors like access to health care facilities and the availability of costly immunomodulatory drugs (IVIG and biologicals), which might affect the outcome in such settings.In addition, the high background rate of infections in such settings presentsclinical challenges in differentiating MIS-C from close mimickers like bacterial sepsis and toxic shock syndrome [10]. Considering these facts, we conducted a single center prospective longitudinal study to describe the clinical, laboratory,echocardiographic findings and follow-up of children with MIS-C in a resource-limited setting.

Methodology

The present study describes the data from 15-07-2020 to 02-06-2021 of a prospective longitudinal study from a tertiary care teaching hospital: the All India Institute of Medical Sciences, New Delhi, India. Children (less than 15 years of age) with fever ≥ 3 days were screened for MIS-C. Those meeting the surveillance definition as per WHO [4] were enrolled for this study after receiving written informed consent from parent/guardian. Children with alternative diagnoses were excluded.All children meeting inclusion criteria were enrolled for the study after taking informed consent. The study was approved by the Institute Ethics Committee (IEC-580/19.06.2020, RP-04/2020).

Evidence of current or preceding SARS-CoV-2 infection was demonstrated either through positive naso-and oro-pharyngeal swab for SARS-CoV-2 nucleic acid using reverse-transcriptase quantitative PCR (RTPCR)/cartridge-based nucleic acid amplification test (CBNAAT) assay or positive serology for antibody (IgG/IgM) using ECLIA (electrochemiluminescence) assay on Elecsys anti-SARS-CoV-2on COBAS 6000 (Roche, Switzerland).

Baseline demographic and clinical data werecollected in a predesigned proforma incorporating the details of clinical, laboratory and echocardiography parameters. The enrolled subjects were managed on broad principles provided by the American College of Rheumatology [11]. The inflammatory markers, markers of myocardial inflammation (Troponin/NT-Pro-BNP), cytokine levels (IL- 2,6,18, TNF-α, INF-γ) in addition to the other laboratory parameters were compared with clinical outcome.The studied cytokines were assayed in serum with Bead-based Multiplex Fluorescent Assay (Luminex ™ technology).

The study subjects were followed up for 4–6 weeks. A 2D- echocardiography was performed at 2 and 4–6 weeks after enrollment.Coronary artery abnormalities were represented as z scores [12]. We also estimated the prevalence of macrophage activation syndrome (MAS) as per the 2016 MAS classification criteria [13].

The data were analyzed using the Stata-12 software. Descriptive statistics was obtained for all study variables. Continuous data were expressed as mean (SD) or median and inter-quartile range [IQR] values. The normality in distribution of data was assessed using the shapriowilk test. Categorical data were expressed as proportions. χ^2 test was used to compare categorical variables. Student t-test was used for comparing normally distributed data, and Mann–Whitney U test was used for comparing non-parametric data. Receiving operative curve analysis was used to find the discriminant ability of serum ferritin and appropriate cutoff for predicting in-hospital mortality. A p value less than 0.05 was considered statistically significant.

Results

We enrolled 31children (19 boys) meeting the WHO criteria of MIS-C [4] during thestudy period. The demographic and laboratory characteristics of the study population has been depicted in Table 1. The mean duration of symptoms was 6.25 days. Twelve children (38.7%) had preexisting chronic comorbidities [systemic lupus erythematosus ($n=1$), Down Syndrome with Tetralogy of Fallot ($n=1$), Transposition of Great Arteries ($n=1$), rheumatic heart disease ($n=1$), acute lymphoblastic leukemia ($n=1$), chronic renal disorder ($n=2$), and neurological (seizure disorder ($n=4$), tubercular meningitis ($n=1$)]. Fever was a universal finding, whereas gastrointestinal (pain abdomen, vomiting and diarrhea) and respiratory symptoms were observed in 71% and 64.3%, respectively. Eighteen children (58.06%) presented with shock, thirteen of whomrequired vasoactive drug support. Seven children (22.5%) required mechanical ventilation,whereas 13 subjects required respiratory support either through a face mask, nasal cannula or high flow nasal cannula. The maculopapular erythematous rash was the most commonly observed skin lesion. We also observed palpable purpura akin to Henoch-Schonlein purpura in a 13-year-girl and gangrene involving the penis and anterolateral aspect of the left leg in an 8-year boy (Fig. 1). Arthritis involving bilateral knee joints was observed in one girl. The inflammatory markers (ESR, CRP and procalcitonin), serum ferritin, IL-6 and cardiac biomarkers (NT-pro BNP) were raised in the study population (Table1).

Table 1 Demographic and laboratory characteristics of children with MIS-C

Parameter	$n=31$
Gender, male (%)	19 (61.29)
Age in months, median(IQR), range	96 (60, 131), 3–181
Duration of illness in days, mean (SD)	6.9 (5.7)
Duration of hospital stay in days, median(IQR)	9 (6.5, 18.5)
Rash, *n* (%)	16 (57.14)
Gastrointestinal symptoms, *n* (%)	22 (70.96)
Respiratory symptoms, *n* (%)	21 (67.74)
Hypotension, *n* (%)	18 (58.06)
Non-purulent conjunctivitis, *n* (%)	8 (25.80)
Mechanical ventilation, *n* (%)	7 (22.5)
Laboratory characteristics	
Either RTPCR/ CBNAAT, *n* (%)	10 (32.26)
Only antibody, *n* (%)	16 (51.61)
Both RTPCR/ CBNAAT and antibody positive	5 (16.13)
Hb (g/dL), median (IQR)	9.31 (8.1, 10.9)
Total leucocyte count (/mm^3), median (IQR)	12,920 (8760, 22,400)
Neutrophils %, median (IQR)	68 (46.3, 84.8),
Lymphocytes %, median (IQR)	23 (9.3, 35)
Platelet count($\times 10^5$/mm^3), median (IQR)	3.48 (1.8, 2.6)
ESR (mm/h), median (IQR)	47 (36, 90)
CRP(mg/dl), median (IQR)	12.8 (3.0, 25.9)
Serum procalcitonin (ng/ml), median (IQR)	8.39 (1.49, 31.89)
Serum ferritin(ng/ml), median (IQR)	411.05 (195.47–1031.93)
D-dimer (ng/ml), median (IQR)	3100 (500, 5250)
Serum fibrinogen (mg/dL), median (IQR)	411.45 (311.16, 466.63)
Serum triglycerides (mg/dL), median (IQR)	218 (125, 406)
SGOT (U/L), median (IQR)	41 (26, 59)
SGPT (U/L), median (IQR)	28 (15, 51)
Blood urea (mg/dL), median (IQR)	38 (19, 68)
Serum creatinine (mg/dL), median (IQR)	0.5 (0.3, 1.06)
NT-pro BNP (pg/mL), median (IQR) (normal < 125 pg/mL)	296.52 (24.66, 4631.31) ($n=15$)
Cytokine profile	
IL-6 (pg/mL),median (IQR) (0.02–10 pg/mL)	59.52 (12.9, 194) ($n=23$)
IL-18 (pg/mL), median (IQR) (9–812 pg/mL)	7.59 (0.87, 94.89) ($n=12$)
IL-2 (pg/mL), median (IQR) (0.03–90 pg/mL)	8.92 (4.21, 53.38) ($n=12$)
INF-γ(pg/mL), median (IQR) (0.6–124 pg/mL)	7 (7, 29.93) ($n=12$)
TNF-α (pg/mL),median (IQR) (0.10–98 pg/mL)	2.5 (2.5, 36.25) ($n=12$)

Four children (12.9%) with multiorgan failure in our cohort succumbed to illness. All of these were RT- PCR positive and had preexisting chronic illnesses [chronic kidney disease ($n=1$), seizure disorder ($n=1$), Downs syndrome with Tetralogy of Fallot ($n=1$), rheumatic heart disease($n=1$)]. Twenty-five children were discharged, and twowere still admitted at the time of drafting this manuscript.

Table 2 compares the various clinical and laboratory parameters in survivors versus those deceased.The serum ferritin levels[median (IQR)] were significantly higher in non-survivors as compared to survivors [1061 (581, 2750) vs 309.5 (140, 720.08) ng/mL, p value = 0.045]. The area under the receiver operator characteristic curve for serum ferritin for in-hospital mortality was 0.82 (95%CI 0.64–0.99) (Online

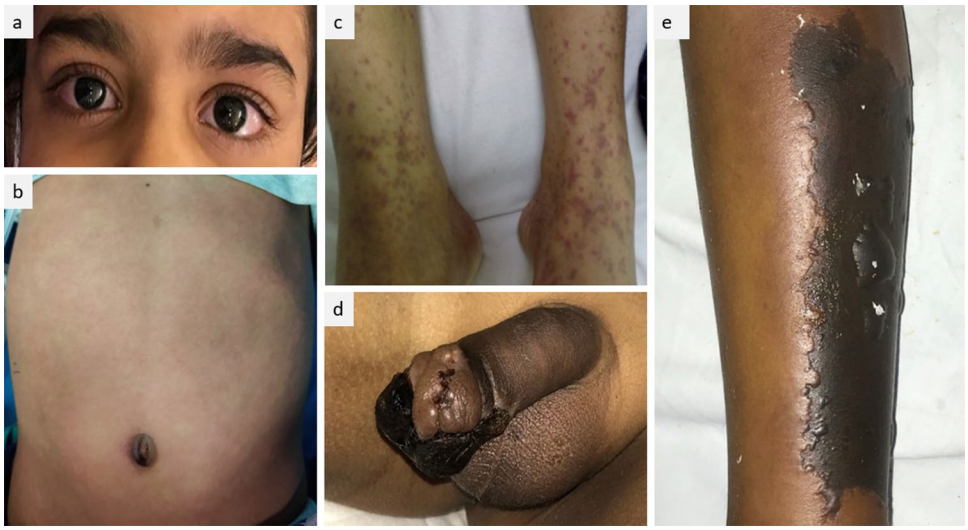

Fig. 1 **a** Bilateral non-purulent conjunctivitis seen in a 6-year-old boy. **b** Generalized erythematous rash noted over the abdomen in a 7-year-old boy. **c** Henoch Schonlein purpura-like non-blanchable palpable purpura seen over bilateral lower limbs in a 13-year-old girl, **d**, **e** Gangrene involving penis and anterolateral aspect of left leg in an 8-year-old boy

Table 2 Comparison of clinical,laboratory parameters and treatment modalities based on mortality in children with MIS-C

	Survivors ($n=27$)	Non-survivors ($n=4$)	p value
Age, Age in months, median(IQR)	96 (60, 120)	130.5 (72, 161)	0.26
Shock, *n* (%)	14 (51.85)	4 (100)	0.12
Gastrointestinal symptoms, *n* (%)	18 (66.66)	4 (100)	0.29
Respiratory symptoms, *n* (%)	17 (62.96)	4 (100)	0.29
Skin rash, *n* (%)	17 (62.96)	0	**0.032**
Pre-existing comorbidity, *n* (%)	8/27	4/4	0.189
Laboratory parameters			
Total leucocyte count, median (IQR)	13,240 (7700, 20,000)	19,685 (12,450, 27,285)	0.51
Platelet count ($\times 10^5/mm^3$), median (IQR)	2.05 (1.5, 3.46)	0.46 (0.17, 2.56)	0.098
Serum IL-6 (5.00–15.0 pg/mL), median (IQR)	41.84 (12.9, 194) ($n=19$)	55.06 (27.06, 328.76) ($n=4$)	0.21
Serum ferritin (12–300 ng/ml), median (IQR)	309.5 (140, 720.08)	1061 (581, 2750)	**0.045**
NT-ProBNP (pg/mL), median (IQR) (< 125 pg/ml)	248.63 (24.66, 3189.7) ($n=13$)	6078.29 (1500.04, 10656.5) ($n=2$)	1.46
D-dimer (ng/ml), median (IQR) (0.00–255.00 ng/ml)	1050 (741.05, 5056) ($n=17$)	4285 (385, 14,035) ($n=4$)	0.16
Immunomodulation therapy			
Supportive care only ($n=5$)	5	0	0.137
Only IVIG ($n=6$)	5	1	
Only steroids ($n=5$)	4	1	
Steroid plus tocilizumab ($n=1$)	0	1	
IVIG plus steroids ($n=14$)	13	1	

Bold represents a statistically significant value ($p \leq 0.05$)

resource 1). At a cutoff value of > 622 ng/ml, the sensitivity and specificity were 75% and 74.1%, respectively.Among the 28 children for whom all laboratory parameters for MAS were available, 5 (17.9%) met the classification for MAS; 2 out of 5 children with MAS succumbed to illness.

Table 3 summarizes the available echocardiography findings of the study population. Coronary artery abnormalities were detected in six children (19.4%); all, except one, resolved at the last follow-up.In our cohort, 8 (25.8%) children met the classification criteria for Kawasaki disease [classical ($n=1$), atypical ($n=7$)].

The various immunomodulatory drugs used in the study population are depicted in Table 2. Two children were referred to us after receiving immunomodulation [only steroids ($n=1$), intravenous immunoglobulins (IVIG), plus steroids ($n=1$)]. IVIG was administered at a dose of 2 g/kg. The infusion was withheld midway after 1 g/kg due to a transfusion reaction in one child. High dose pulse methylprednisolone (10–30 mg/kg/day for 3 days) followed by oral steroids was administered to 4 subjects.Oral steroids (prednisolone @ dose of 2 mg/kg/day) were gradually tapered over 2–3 weeks. Two children required a prolonged course

Table 3 Baseline and follow-up echocardiography in children with MIS-C

Echo parameter	Baseline	Echo at 2-week follow-up	Echo at 4 to 6-week follow-up
Number of children with low ejection fraction (EF ≤ 55%), *n*	13/29	1/16	4/12
Ejection fraction, mean (SD)	55.75 (9.24)	59.18 (7.97)	57.75(4.45)
Coronary artery abnormalities, *n*	RCA*: 2/19 LMCA:0/20 LAD#:1/11	RCA: 0/14 LMCA$:1/12 LAD$:1/10LCx$:1/12	RCA: 0/12 LMCA:0/12 LAD:0/4
Any other	LCx wall thickening (*n* = 1) Peri-vascular brightness (*n* = 1)	Peri-vascular brightness (*n* = 1)	–
Valvular regurgitation	Mild MR and TR:3/28 Mild MR: 1/28 Mild TR:1	Mild MR and TR (*n* = 1)	Mild TR (*n* = 2)
Pericardial effusion, n	Mild (*n* = 1)	0	0
Any other abnormality	–	–	Mild PAH (*n* = 1)

Z-score

One child had RCA z score of *2.15

One child had z scores of RCA and LAD 3.17 and # 2.53 respectively

$Same child, LAD: 5.2, LMCA and LCx dilated

Dilation or Aneurysm based on Z scores

Dilation (*z* score 2–2.5)

Small (*z* score 2.5–5)

Medium (*z* score 5–10)

Giant (*z* score > 10)

LAD Left Anterior Descending artery, *LMCA* Left Main Coronary artery, *LCx* Left Circumflex artery, *TR* Tricuspid Regurgitation, *MR* Mitral Regurgitation, *PAH* Pulmonary Arterial Hypertension

(> 3 months) of oral prednisolone due to the possibility of evolving rheumatic disorder. There was no statistically significant difference in mortality based on the choice of immunomodulatory agent (*p* value = 0.137). Twelve subjects received aspirin in antiplatelet doses for 4–6 weeks. In addition, two children required enoxaparin: one with low ejection fraction received it for a week while the other with penile gangrene and venous thrombosis (involving right saphenofemoral junction and deep veins of the calf in bilateral lower limbs) was still on enoxaparin at the last follow-up at 12 week. All children also received empirical broad-spectrum antibiotics; however, the blood cultures were sterile in all subjects.

Discussion

This study reports the clinical, laboratory profile and outcomes at short-term follow-up of children with MIS-C from India. During the study period, 31 children with MIS-C were enrolled. In addition to the usual clinical features, HSP like rash, penile gangrene and arthritis were few uncommon findings in our cohort. Baseline coronary artery abnormalities were observed in 6 (19.4%) subjects, which resolved in all except one at the last follow-up. Four children (12.9%) with underlying chronic comorbidities succumbed to the illness.

All our subjects were either RTPCR/ CBNAAT positive or antibody positive, unlike other series from tropical countries wherein children with a history of contact (without laboratory evidence to support an association with SARS-CoV-2) were also enrolled (27% in Dhanalakshmi et al. and 34% in Jain et al. series) [14, 15]. In the authors' opinion, laboratory evidence of SARS-CoV-2 infection adds strength to the inclusion criteria while classifying febrile children as MIS-C and may avoid over-diagnosis of MIS-C. This is more relevant to tropical countries where the background infections mimicking MIS-C are widely prevalent.

Similar to the existing literature,the spectrum of illness in our series varied from non-life-threatening febrile episodes to severe illness resulting in cardiovascular collapse and shock [16]. Nearly 60% of our study population presented with shock, comparable to various series from different parts of the globe [3, 17]. In 64% of children, respiratory symptoms were seen, two-thirds of whom required non-invasive oxygen support, while a third of these required mechanical ventilation. Gastrointestinal symptoms (mild to moderate severity) were seen in around 71% of children. Twelve of the 31 children had underlying

systemic comorbidity. Ahmad et al. in their systematic review reported a significant proportion of comorbidities with obesity accounting for half of the associated comorbidities [18], which is in contrast to our series where only 2/31 (6.45%) were obese (results not shown).

We also observed few peculiar findings in our series. A 13-year-old girl presented with a rash similar to IgA vasculitis. She also had pain abdomen but did not have other features consistent with IgA vasculitis; neither did she develop recurrence of symptoms or renal involvement during 6 months of follow-up. Allez et al. have previously reported the association of IgA vasculitis with COVID-19 in a young adult with Crohn's disease on anti-TNF [19]. Although we couldn't contemplate skin biopsy in our case, the palpable purpura was clinically similar to HSP. Another girl with an underlying seizure disorder presented with arthritis of bilateral knee joints. The workup for the evolution of other rheumatic diseases, such as lupus, was non-contributory till the last follow-up. These observations are in sync with the emerging evidence of other vasculitis and rheumatic disorders in association with COVID-19 [18], and thus, it is imperative to note such clinical findings and follow these children for the evolution of immune manifestations. An 8-year-old boy developed penile gangrene with deep vein thrombosis requiring prolonged anticoagulation. Thrombosis is frequently reported in adults with COVID-19 but is an uncommon finding in children [20]. Feldstein et al. have reported one child with imaging confirmed symptomatic venous thromboembolism [21]. The index child in our series was aptly managed with immunosuppression and anticoagulants. These gangrenous changes may result from ischemic changes, resulting from vascular insult and necrosis of SARS-CoV-2 infected endothelial cells. Kabeerdosset al. have proposed this mechanism for COVID associated chillbains or COVID toes [10].Timely recognition and management of such organ/limb-threatening thrombotic complications are warranted for a successful outcome.

The median values of laboratory markers of cardiac involvement (NT-pro-BNP) were elevated in the study population (Table 1). Markers of cardiac injury like Troponin and BNP are elevated in 64–95% of children with MIS-C in various series [17]. Aliased et al. in their review, reported wide variability in left ventricular dysfunction, ranging from 20% to nearly all, in various series [17]. Coronary artery abnormalities have been reported in 8–24% of cases in other series [9]. In our series, six patients (19.3%) had coronary involvement. There is a scarcity of data about follow-up outcomes. Echocardiography demonstrated a low ejection fraction (< 55%) in 44.8% of the subjects, which decreased to 33.3% at 4–6 weeks follow-up.The short-term outcome for coronaries was reassuring in our series; the coronary artery abnormalities resolved in 5 out of 6 children.

Among the clinical and laboratory factors studied in our series, serum ferritin levels were significantly higher in those who succumbed. Fifty percent of the children who succumbed to illness had MAS. This finding is consistent with a large retrospective study from the US by Abrams et al. [22], comprising 1080 children wherein ferritin was found to be an indicator of shock and cardiovascular compromise. Serum ferritin may also help in differentiating MIS-C from its close mimicker Kawaski disease; Yener et al. reported higher serum ferritin levels in children with MIS-C as compared to KD [440 ng/ml versus 170 ng/ml in MISC and KD respectively] in a multicentric Turkish study, enrolling 154 children with MIS-C and 59 children with KD [23]. Similar to Yener et al. study, we also obsereved an elevated serum ferritin levels [median 411.45 (311.16, 466.63) ng/ml)] in our cohort.

We also observed raised levels of IL-6 in the mortality group as compared to survivors; however, the difference was not statistically significant, unlike Abrams et al. series describing an association of increased risk of hemodynamic compromisewith IL-6 levels;the small sample size in the present series might have resulted in varying observations.

The high mortality rate (12.9%) observed in the present series is in stark contrast to that reported from multi-hospital data from US [8, 21]. The reported mortality in Indian series ranges from 0 to 27.5% [14, 15, 24]. All children who succumbed to illness in our series had underlying comorbidities, which might have contributed to poor outcomes. The only series reporting higher mortality (27.5%) than ours, by Maheshwari et al. didn't mention about the underlying comorbidities. The other speculated factors contributing toincreased mortality in resource-poor settings include delayed referral to tertiary care centers and delay in instituting timely immunomodulation [24].

Our study has certain limitations, including a small sample size, which precludes us from undertaking a subgroup analysis in children receiving various immunomodulatory drugs. In addition, our center, a tertiary care referral hospital, may not reflect the overall spectrum of MIS-C, and the results may not be generalizable. Although the mortality is high compared to other series, the absolute number is small to make meaningful conclusions on the predictors of mortality.

Conclusion

The underlying hyper-inflammation in MIS-C causes acute hemodynamic deterioration in most children.Children with MIS-C can present with unusual findings such as HSP like rash, gangrene and arthritis. In children without any premorbid conditions, the outcome is usually optimistic.Raised ferritin level may be a poor prognostic marker. The follow-up at

4–6 weeks for coronary artery outcomes is reassuring.Large multi-centric follow-up studies are required to delineate the best therapeutic modalities and predictors of outcome; particulary in resource-limited settings.

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Declarations

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval Approved by the institute ethics committee (IEC-580/19.06.2020, RP-04/2020).

Data availability All data and material are available with the corresponding author.

Code availability Available with the corresponding author.

Consent for participation Consent obtained from the parents of all enrolled children at the time of enrollment in the prescribed participation consent form.

Consent for publication Consent obtained from the parents of all enrolled children, as well as the authors.

References

1. Liu W, Zhang Q, Chen J, Xiang R, Song H, Shu S et al (2020) Detection of Covid-19 in children in early January 2020 in Wuhan, China. N Engl J Med 382(14):1370–1371
2. Belhadjer Z, Méot M, Bajolle F, Khraiche D, Legendre A, Abakka S et al (2020) Acute heart failure in multisystem inflammatory syndrome in children (MIS-C) in the context of global SARS-CoV-2 pandemic. Circulation 142(5):429–436
3. Verdoni L, Mazza A, Gervasoni A, Martelli L, Ruggeri M, Ciuffreda M et al (2020) An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. Lancet 395:1771–1778
4. World Health Organization. Multisystem inflammatory syndrome in children and adolescents with COVID-19. Scientific brief (2020). (https://www.who.int/publications/i/item/multisystem-inflammatory-syndrome-in-children-and-adolescents-with-covid-19)
5. Centers for Disease Control and Prevention. Emergency preparedness and response: multisystem inflammatory syndrome in children (MIS-C) associated with coronavirus disease 2019 (COVID-19). Health advisory (2019). (https://emergency.cdc.gov/han/2020/han00432.asp. opens in new tab)
6. Royal College of Paediatrics and Child Health. Guidance: paediatric multisystem inflammatory syndrome temporally associated with COVID-19 (2020). https://www.rcpch.ac.uk/resources/guidance-paediatric-multisystem-inflammatory-syndrome-temporally-associated-covid-19. Accessed 22 May 2020
7. Whittaker E, Bamford A, Kenny J, Kaforou M, Jones CE, Shah P et al (2020) Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. JAMA 324(3):259
8. Son MBF, Murray N, Friedman K, Young CC, Newhams MM, Feldstein LR et al (2021) Multisystem inflammatory syndrome in children—initial therapy and outcomes. N Engl J Med. https://doi.org/10.1056/NEJMoa2102605
9. Valverde I, Singh Y, Sanchez-de-Toledo J, Theocharis P, Chikermane A, Di Filippo S et al (2021) Acute cardiovascular manifestations in 286 children with multisystem inflammatory syndrome associated with COVID-19 infection in Europe. Circulation 143(1):21–32
10. Kabeerdoss J, Pilania RK, Karkhele R, Kumar TS, Danda D, Singh S (2021) Severe COVID-19, multisystem inflammatory syndrome in children, and Kawasaki disease: immunological mechanisms, clinical manifestations and management. Rheumatol Int 41(1):19–32
11. Henderson LA, Canna SW, Friedman KG, Gorelik M, Lapidus SK, Bassiri H et al (2020) American College of rheumatology clinical guidance for multisystem inflammatory syndrome in children associated With SARS–CoV-2 and hyperinflammation in pediatric COVID-19: version 1. Arthritis Rheumatol 72(11):1791–1805
12. McCrindle BW, Li JS, Minich LL, Colan SD, Atz AM, Takahashi M et al (2007) Coronary artery involvement in children with Kawasaki disease. Circulation 116(2):174–179
13. Ravelli A, Minoia F, Davì S, Horne A, Bovis F, Pistorio A et al (2016) 2016 Classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: a European League Against Rheumatism/American College of Rheumatology/Paediatric Rheumatology International Trials Organisation Collaborative Initiative. Arthritis Rheumatol 68(3):566–576
14. Dhanalakshmi K, Venkataraman A, Balasubramanian S, Madhusudan M, Amperayani S, Putilibai S et al (2020) Epidemiological and clinical profile of pediatric inflammatory multisystem syndrome—temporally associated with SARS-CoV-2 (PIMS-TS) in Indian children. Indian Pediatr 57(11):1010–1014
15. Jain S, Sen S, Lakshmivenkateshiah S, Bobhate P, Venkatesh S, Udani S et al (2020) Multisystem inflammatory syndrome in children with COVID-19 in Mumbai, India. Indian Pediatr 57(11):1015–1019
16. Jiang L, Tang K, Levin M, Irfan O, Morris SK, Wilson K et al (2020) COVID-19 and multisystem inflammatory syndrome in children and adolescents. Lancet Infect Dis 20(11):e276–e288
17. Alsaied T, Tremoulet AH, Burns JC, Saidi A, Dionne A, Lang SM et al (2021) Review of cardiac involvement in multisystem inflammatory syndrome in children. Circulation 143(1):78–88
18. Ahmed M, Advani S, Moreira A, Zoretic S, Martinez J, Chorath K et al (2020) Multisystem inflammatory syndrome in children: a systematic review. EClinicalMedicine 26:100527
19. Allez M, Denis B, Bouaziz J, Battistella M, Zagdanski A, Bayart J et al (2020) COVID-19–Related IgA vasculitis. Arthritis Rheumatol 72(11):1952–1953

20. Levi M, Thachil J, Iba T, Levy JH (2020) Coagulation abnormalities and thrombosis in patients with COVID-19. Lancet Haematol 7(6):e438–e440
21. Feldstein LR, Tenforde MW, Friedman KG, Newhams M, Rose EB, Dapul H et al (2021) Characteristics and outcomes of US children and adolescents with multisystem inflammatory syndrome in children (MIS-C) compared with severe acute COVID-19. JAMA 325(11):1074
22. Abrams JY, Oster ME, Godfred-Cato SE, Bryant B, Datta SD, Campbell AP et al (2021) Factors linked to severe outcomes in multisystem inflammatory syndrome in children (MIS-C) in the USA: a retrospective surveillance study. Lancet Child Adolesc Health 5(5):323–331
23. OtarYener G, PaçKısaarslan A, Ulu K, Atalay E, Haşlak F, Özdel S et al (2021) Differences and similarities of multisystem inflammatory syndrome in children, Kawasaki disease and macrophage activating syndrome due to systemic juvenile idiopathic arthritis: a comparative study. Rheumatol Int 27:1–7. https://doi.org/10.1007/s00296-021-05008-w
24. Maheshwari A, Mahto D, Kumar V, Gulati S, Pemde H, Saha A et al (2021) Comparison of clinical and laboratory profile of survivors and non-survivors of SARS-CoV-2-related multisystem inflammatory syndrome of childhood in India: an observational study. J Paediatr Child Health. https://doi.org/10.1111/jpc.15675