ORIGINAL ARTICLE

Clinical and Laboratory Profile of Macrophage Activation Syndrome in Kawasaki Disease: A Single Centre Cross-Sectional Study

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ABSTRACT

Objective: To study the prevalence of Macrophage Activation Syndrome (MAS) in children with Kawasaki disease (KD) and to devise a classification tree for predicting MAS in early KD based on easily available clinical and laboratory information using artificial intelligence (AI) technology.

Methods: A prospective cross-sectional observational study was conducted (March 2020 – October 2021) during which hospitalized children aged 1-18 years with KD were consecutively enrolled. Those with positive RTPCR test or IgM/IgG serology for COVID-19 were excluded. The clinical and laboratory profiles of children with and without MAS were studied. A multivariable logistic regression (LR) model was developed utilizing backward elimination method to determine the relationship between select candidate predictor variables and MAS in patients with KD. A classification tree was created based on these using artificial intelligence algorithms.

Results: Sixty-two children were diagnosed with KD during the study period, of these, 42 children with KD were included; 14 (33.3 %) were diagnosed with MAS. The median (IQR) duration of fever (days) was significantly more in MAS than those without MAS [7 (5, 15) vs 5 (5, 9), $P < 0.05$]. Serum albumin (g/dL) was significantly lower in those with MAS [2.3 (2.2, 2.7) vs 2.8 (2.3, 3.1), $P = 0.03$]. The classification tree constructed by the AI-based algorithm predicted that in children with KD who had myocardial dysfunction, serum albumin ≤ 2.8 g/dL and fever > 6 days duration at admission had increased likelihood of developing MAS. In children without myocardial dysfunction, alanine transaminase (ALT) levels > 70 U/L and fever > 5 days were equally predictive of MAS.

Conclusion: Nearly one-third of the children with KD had MAS. Clinicians should consider screening all children with KD for MAS at admission. A classification tree based on the presence of myocardial dysfunction, duration of fever > 6 days, ALT levels and hypoalbuminemia can identify MAS in the course of KD.

Keywords: *Albumin, immunomodulation, myocardial dysfunction, classification tree*

INTRODUCTION

Kawasaki disease (KD) is a medium vessel vasculitis with an increased predilection for coronary artery involvement that is seen predominantly in young children [1]. Physicians have to rely on clinical signs and symptoms like fever, rash, mucocutaneous changes and lymphadenopathy for establishing a diagnosis, as there are no confirmatory laboratory tests. Due to a varied presentation and a considerable overlap in clinical features of atypical KD and other tropical infections like measles, chikungunya or dengue, diagnosis of KD can be challenging [2,3]. Timely recognition is essential as delayed diagnosis and treatment may not only result in life-threatening systemic complications like shock, myocarditis, acute kidney injury (AKI), multi-organ dysfunction syndrome (MODS) and macrophage activation syndrome (MAS), but also lifelong cardiac sequelae [3].

Macrophage activation syndrome is a secondary hemophagocytic lymphohistiocytosis (HLH) syndrome usually described in the context of systemic onset juvenile idiopathic arthritis (SOJIA), systemic

lupus erythematosus (SLE) and also (unknown to many clinicians) KD. Concurrent KD and MAS is associated with higher rates of coronary artery abnormalities [4,5] and mortality (13%) than isolated KD [6]. Recognition of coexisting MAS in KD is pertinent as timely administration of high dose pulse corticosteroid therapy, infliximab and/or cyclosporine has better prognosis [6,7].

The prevalence of MAS in KD was reportedly 1-2 % [5-7] before the COVID-19 pandemic. However, since the COVID-19 pandemic, Verdoni et al and Riphagen et al reported a 30-fold increase in the incidence of KD, and a higher prevalence of concurrent MAS (up to 50%), respectively [9,10]. This trend was also observed in our institute which prompted us to start screening all patients with KD for MAS at admission. As per the International Consensus Criteria, the diagnosis of MAS requires testing for additional laboratory parameters like serum ferritin, fibrinogen and triglyceride levels [11]. However, these may not be easily available in low resource settings leading to a delayed or missed diagnosis of MAS. Given this background, the aim of this prospective study was to determine the proportion of children with KD identified with concurrent MAS at presentation. We also attempted to create an artificial intelligence (AI) based clinical decision algorithm that would help identify MAS in KD using preliminary clinical and laboratory parameters that are available even in resource-limited centers.

METHODS

This cross-sectional observational study was conducted in a tertiary care hospital in North India from March 2020 to October 2021 after obtaining approval from the Institutional Ethics Committee. All consecutive children aged 1 month to 18 years, presenting to our hospital with fever ≥ 5 days and clinical features of KD as per American Heart Association (AHA) 2017 criteria were enrolled [1]. We also included children who satisfied criteria for incomplete or atypical KD [1]. We excluded children with positive serology or real-time reverse transcriptase-polymerase chain reaction (RT-PCR) for Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) to rule out possible confounding cases of multisystem inflammatory syndrome in children (MIS-C) [12]. Written informed consent or assent was obtained from caregivers. We calculated a sample size of 42 participants based on assumed prevalence of MAS in KD as 50% [9], margin of error 15%, confidence level 95%, and alpha error of 0.05.

The following study specific details of all participants were recorded in a standardized proforma: clinical manifestations; investigation results of ferritin, fibrinogen, triglycerides, quantitative D-dimer, and N terminal pro-B-type natriuretic peptide (NT-pro BNP) and two-dimensional echocardiography (performed by a pediatric cardiologist), and management. Standard definitions were used for known complications. Myocardial dysfunction was defined as shock in the presence of indicators of myocardial injury: elevated biochemical markers i.e., CPK-MB > 45 IU/L, NT-pro BNP > 500 pg/mL, or positive Troponin-T (commercial colorimetric kit), or; echocardiographic evidence of myocardial dysfunction. Acute kidney injury was determined as per the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 definition [12]. MAS was defined according to Ravelli's International Consensus Criteria [13] i.e., ferritin > 685 mg/L with two of the following abnormal laboratory parameters: platelet count ≤ 1.81 x 10^9/L; serum aspartate transaminase (AST) > 48 U/L; triglyceride > 156 mg/dL, and; fibrinogen ≤ 360 mg/dL. Significant dilatation

of the right coronary artery, left main coronary artery and/or left anterior descending artery on echocardiography was defined according to *z*-scores [1].

Therapeutic details included the first-line immune-modulator used, its dose and time taken for response (resolution of fever), and need for second line drugs with indication. All patients received intravenous immunoglobulin (IVIG, 2 g/kg over 12 - 18 hours), aspirin (50 mg/kg/day for 48 hours, followed by 5 mg/kg/day) and prednisolone (2 mg/kg/day for 2 weeks with slow tapering). The children with MAS also received pulse IV methylprednisolone (30 mg/kg/day for 5 days) followed by tapering with prednisolone. Second-line drugs (cyclosporin, atorvastatin or infliximab) were provided when indicated as per institutional protocol [7].

Statistical analysis: Descriptive statistics was used for qualitative data. Clinical and laboratory parameters were compared using Chi square or Fisher exact test in KD with and without MAS, depending on the normality of data. Logistic regression (LR) analysis was used for predicting odds of MAS in KD using generalised linear model (GLM) function for binomial family with logit link in R software version 4.1.0. Initially simple LR analysis was performed to derive unadjusted odds of known predictors, which were selected after an exhaustive literature review including the 2017 AHA guidelines [1]. These included age, duration of fever, presence of infections, central nervous system (CNS) dysfunction, shock, AKI, myocardial dysfunction, hemoglobin, C- reactive peptide, serum albumin and presence of elevated ALT (>70 U/L). Age was the only quantitative predictor which followed a linear relation with log-odds of MAS in KD. Hence, the remaining quantitative predictors were categorised as hemoglobin ≤ 7 g/dL, C reactive protein ≥ 100 mg/L, and serum albumin ≤ 2.5 g/dL for further evaluation in LR. The duration of fever was categorised into ≥ 7 days, ≥ 10 days and ≥ 14 days [5-7]. Predictors having coefficients of unadjusted odds with *P* value < 0.25 were selected for multivariable LR to determine the adjusted odds using backward elimination method (to preserve precision). The first predictive model was made with all predictor variables with *P* value < 0.25. The variable with the maximum *P* value was dropped, and the next model was made with the remaining variables. This process continued until all the variables were statistically significant and a model was built with the best area under receiver operating characteristic curve (AUROC). Goodness of fit of each model was compared with the previous one by ANOVA test and likelihood ratio test.

Since our sample size for regression was sub-optimal for secondary analysis, we performed classification modelling using the C.50 package based on AI algorithms. This built a classification tree that identified features in patients that were specific for MAS in KD using the seven variables selected for multivariable LR. Eighty percent of the data was divided into a training set and the remaining 20% into a testing set. The almost equal proportions of patients with MAS in both sets ensured proper randomization. The model was trained on to the training set and a final classification tree was plotted using machine-learning algorithms. The performance of this model was evaluated on the testing set, with construction of a confusion matrix to derive sensitivity, specificity, precision, accuracy and error rates.

RESULTS

Of the 62 patients who were diagnosed with KD, 20 were excluded due to IgM and/or IgG positivity for SARS CoV-2 **(Fig. 1).** The study population comprised of 42 patients; 29 (69%) children with incomplete

KD and 13 (31%) with complete KD. MAS was identified in 14 (33%) cases. The clinical and laboratory profiles of all patients are summarized in **Table I,** with an embedded comparison of children with and without MAS**.** The proportion of incomplete KD was 11 (64.7%) and 18 (72%) in both, respectively. Nine children (6 MAS and 3 non-MAS) had IVIG resistance (recurrence of fever after 36 hours completion of IVIG) [1] that required a single infliximab infusion (5 mg/kg). No mortality was observed during the study duration.

The five predictive models are depicted in **Table II.** Model 5 had an AUROC of 0.8, best Akaike information criterion (AIC) value of 52.48, and did not display loss of information by ANOVA and likelihood ratio test. The regression equation was as follows: 'ln (Odds of having MAS) = - 2.03 + 2.67 *a + 1.33 *b + 1.38 *c': wherein, 'a' is 1 if fever ≥ 14 days, and 0 if fever < 14 days; 'b' is 1 if serum albumin ≤ 2.5 g/dL, and 0 if serum albumin > 2.5 g/dL, and; c is 1 if ALT > 70 U/L, and 0 if ALT < 70 U/L. The generated classification tree with seven terminal nodes is shown in **Fig. 2.** Terminal node 6 (n = 2) and 12 (n = 7) included 9 out of the total 14 patients with MAS which made the use of the 'if- then sequential classification rules' to predict MAS in KD applicable. Sensitivity, specificity, positive predictive value, accuracy and misclassification were 75%, 100%, 100%, 88.89% and 11.11%, respectively.

DISCUSSION

A published systematic review in the pre-COVID-19 pandemic period on MAS in KD reports only 67 patients derived from multiple sources worldwide, out of which three-fourth were diagnosed later in the course of disease [6]. To the best of our knowledge based on an exhaustive review of literature, this study reports the largest number of children with KD and MAS from a single centre. This is probably due to the fact that we screened all children with KD for MAS. In addition, our study was conducted during the pandemic and the change in immunological dysregulation secondary to COVID-19 could theoretically have led to more severe phenotypes of KD including concurrent MAS [9,10]. The incidence of MAS in pre-pandemic KD may not be a true representation as universal screening for MAS was not practiced [3-7] and children were investigated only after a clinical suspicion arose based on the progression and severity of illness in the presence of hepatosplenomegaly, cytopenia and coagulopathy.

Our study population of children with KD comprised of similar proportions below 5 years as observed in existing literature, though the median age of presentation was much lower (24, IQR 9, 72 months). The male-to-female ratio of 2:1 was similar to previous Indian studies [14,15]. In literature, most reported patients of KD with MAS are older than 5 years of age [3,4-7], but we observed a median age of 4 years (range 2-72 months). An increase in prevalence and age-related downward shift was also observed during the pandemic in Subacute sclerosing panencephalitis (SSPE), a known immune-mediated illness, that was hypothesized to be triggered by some unidentified factor that resulted in immune dysregulation [16]. Whether this applies to cytokine-mediated MAS needs to be explored further.

We found a significant association of hypoalbuminemia in children with MAS that may be due to two reasons. Firstly, increased albumin leakage is known to occur in the acute phase of illness. Secondly, albumin is a negative acute phase reactant in systemic inflammatory reaction that results from the unbridled cytokine storm observed in MAS [5-7]. Earlier studies have reported thrombocytopenia and hyperferritinemia

as biomarkers suggesting underlying MAS [3-7,13]. In the present study ferritin levels were significantly higher in KD with MAS, but platelet counts were not significantly lower. We also did not find any association of hypertriglyceridemia, hypofibrinogenemia and hyponatremia in either of the subgroups of KD; with and without MAS. This may be explained by the fact that these findings usually occur later in the course of disease, whereas our patients were identified relatively earlier. Thus, these clinical biomarkers may not have been unveiled. Coronary artery aneurysms (CAA) can be present in 25% cases of untreated KD, which decreases to 4% with IVIG therapy [1]. Existing literature shows that MAS may be an underlying risk factor for CAA with the prevalence reportedly higher (10–50%) in patients with KD and MAS [1,7,17-18]. We observed a similar increase in the subgroup of KD with MAS, albeit this was not statistically significant. None of our cases had any residual CAA during a 12-month follow-up, presumably due to the early aggressive therapy.

The large number of cases of KD in our study made it feasible for us to construct a clinical prediction model for early assessment of MAS in KD. The LR modelling was performed to determine the relation (if any) between the select predictor variables derived from existing literature and the probability of MAS in KD**.** The AI-based algorithm provides a simple 'yes/no' and 'if –then' flowchart to predict MAS in KD using baseline clinical and laboratory parameters. Significantly, our classification tree modelling can identify MAS patients 'very early' in the natural history of illness, is simple to use, and will help clinicians identify MAS that will facilitate timely addition of high dose corticosteroids to the standard therapeutic regimen. Our algorithm shows that the presence of all three parameters (myocardial dysfunction, hypoalbuminemia, and fever > 6 days) have a 100% likelihood of having MAS. Similarly, it also demonstrates equal likelihood of MAS when the fever is more than 5 days, the ALT is raised (> 70 U/L) and there is no myocardial dysfunction **(Fig. 1)**. This algorithm is in alignment with the pre-pandemic evidence, which indicates that in patients with KD aged more than 5 years, fever persisting for more than 10 days and incomplete KD is highly predictive of underlying MAS [4-6]. These findings along with the evidence corroborates our model and makes it biologically plausible. It is important to realize that this model is valid even now when the pandemic is over, since the most common reason for underdiagnosis of KD is lack of clinical suspicion. Thus, the use of this model at admission will help in increasing detection.

Despite the fact that we had a large number of children with MAS in KD from a single center, the sample size was still not adequate for multivariable LR modelling. This limitation was offset by the method by which the AI algorithm-based classification tree was modelled by dividing the data based on the seven parameters selected in the final model of LR. Though this model is biologically plausible, and backed by supportive scientific evidence, and sensitivity, specificity, positive predictive value and accuracy appear to be acceptable, these results will need to be tested and validated on larger data sets. Further research using a multicentric design with adequate sample size and patients identified in the early clinical course would be the next logical step forward.

We observed encouraging benefits by changing our policy to universal early screening for MAS in children with KD. These included early recognition, timely therapy of MAS in addition to treatment of KD, and good outcomes with no mortality. Based on this, we propose that clinicians consider screening for MAS

in KD at initial presentation The use of the proposed classification tree with easily available clinical information (duration of fever, myocardial dysfunction, ALT and serum albumin) may be helpful in predicting MAS early in the course of disease.

Contributors: AM, SG: Study design, acquisition, analysis and interpretation of data, drafting the manuscript; VK, KDR: Data acquisition, tabulating results and review of literature; AM: Conceived the idea, critical revision of manuscript at all its stages, final approval of manuscript; SG: Statistical analysis along with the logistic regression and formulation of the final model; MA: Laboratory analysis. SB, DM: Contributed to analysis and interpretation of data. All authors critically reviewed and approved the final manuscript.

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WHAT THIS STUDY ADDS

- All children with Kawasaki Disease (KD) should be screened for macrophage activation syndrome (MAS)
- Early identification of MAS translates into timely treatment with high dose pulse methylprednisolone in addition to standard treatment of KD that is associated with better outcomes.
- An artificial intelligence-based algorithm using easily available clinical information (duration of fever, markers of myocardial injury, ALT and serum albumin) may predict MAS early in the course of illness.

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Table I Clinical and laboratory profile of children with Kawasaki Disease with and without Macrophage Activation Syndrome (MAS)

Parameters	*Children with KD* (*n* =42)	*MAS* (*n* = 14)	*Non-MAS* (*n* = 28)	*P value*
Clinical Characteristics				
Age (months)[a]	24 (9, 72)	48 (2, 72)	24 (12, 72)	0.7
Male	28 (66.7)	11 (64.7)	17 (68)	1
Duration of fever (days)[a]	6 (5, 10)	07 (5, 15)	05 (5, 9)	0.04
Rash	25 (59.5)	10 (58.8)	15 (60)	1
Mucositis	20 (47.6)	08 (47)	12 (48)	1
Lymphadenopathy	9 (21.4)	03 (17.6)	06 (24)	0.72
Eye redness	22 (52.3)	11 (64.7)	11 (44)	0.32
Desquamation of the skin	8 (19.0)	5 (29.4)	03 (12)	0.23
IVIg resistance	9 (21.4)	6 (40)	3 (10)	0.025
Acute kidney injury	9 (21.4)	06 (35.3)	03 (12)	0.12
Liver dysfunction	16 (38.1)	09 (52.9)	07 (28)	0.19
Shock	22 (52.4)	11 (64.7)	11 (44)	0.32
Myocardial dysfunction	17 (40.4)	10 (58.8)	07 (28)	0.09
Coronary Artery Aneurysm	7 (16.6)	03 (21.4)	04 (14.2)	0.40
CNS dysfunction	4 (9.5)	03 (17.6)	01 (4)	0.29
Laboratory parameters[a]				
Hemoglobin (g/dL)	9.5 (7.9, 10.2)	9.7 (7.9, 10.4)	9.5 (7.9, 10.2)	0.48
TLC (x 10^9/L)*	11.5 (8.3, 20.1)	11.2 (7.7, 25)	13.4 (8.6, 18.3)	0.59
Platelet count (x10^9/L)	180 (107, 267)	140 (100, 590)	230 (127, 260)	0.75
CRP (mg/L)	130 (57.5, 211.5)	114 (56, 205)	130 (60, 213)	0.64
D-dimer (ng/mL)	1170 (701.5, 2100)	1980.5 (768.5, 2150)	1068.5 (555.75, 1915.75)	0.75
Fibrinogen (mg/dL)	345 (193, 403)	378 (248, 446)	390 (346, 466)	0.32
Albumin (g/dL)	2.8 (2.4, 3.1)	2.3 (2.2, 2.7)	2.8 (2.3, 3.1)	0.03
Triglyceride (mg/dL)	220 (174.5, 308.5)	136 (123, 212)	134 (116, 177)	0.69

CNS Central nervous system, CRP C-reactive protein, TLC Total leukocyte count
Values expressed as n (%), [a]median (IQR)
**No case of cytopenia was seen*

Table II: Predictors of Macrophage Activation Syndrome in Kawasaki Disease

Predictor[a]	*Unadjusted Odds Ratio (95% CI)*	*Model 1*	*Model 2*	*Model 3*	*Model 4*	*Model 5*
Fever ≥ 14 days	10 (1.4, 203.3)	12.2 (0.8, 374.2)	12.3 (1.0, 347.1)	12 (1.2, 328.1)	14.4 (1.4, 390.4)	14.4 (1.6, 351.1)
S Albumin ≤ 2.5 g/dL	3.6 (1.0, 14.4)	3.4 (0.6, 19.2)	3.3 (0.7, 17.7)	3.4 (0.8, 17.6)	3.58 (0.8, 18.5)	3.8 (0.9, 18.8)
Myocardial dysfunction	3.6 (1.0, 14.2)	2.2 (0.2, 24.3)	2.2 (0.4, 11.5)	2.2 (0.5, 10.3)	2.2 (0.5, 10.3)	
Acute kidney injury	4 (0.8, 21.9)	1.7 (0.3, 12.79)	1.7 (0.2, 12.6)	1.8 (0.3, 12.6)		
CNS dysfunction	5.1 (0.5, 109.6)	0.8 (0.04, 31)	0.8 (0.04, 30.0)			
Shock	2.3 (0.6, 8.7)	0.9 (0.08, 9.6)				
ALT ≥ 70 U/L	2.8 (0.8, 10.9)	2.7 (0.4, 18.5)	2.8 (0.5, 17.6)	2.7 (0.5, 16.2)	3.4 (0.8, 17.7)	3.9 (0.9, 20.0)
Baseline odds (Exponentiated odds)		0.1 (0.01, 0.4)	0.1 (0.02, 0.4)	0.1 (0.02, 0.4)	0.1 (0.02, 0.4)	0.1 (0.03, 0.5)
(AUROC)	-	0.79	0.79	0.79	0.79	0.78
(AIC)	-	58.976	56.976	54.983	53.369	52.478

AIC Akaike information criterion, ALT Alanine transaminase, AUROC Area under receiver operating characteristic curve, CNS Central nervous system

[a]*The seven variables selected on simple LR by virtue of unadjusted odds ratios with* $P < 0.25$

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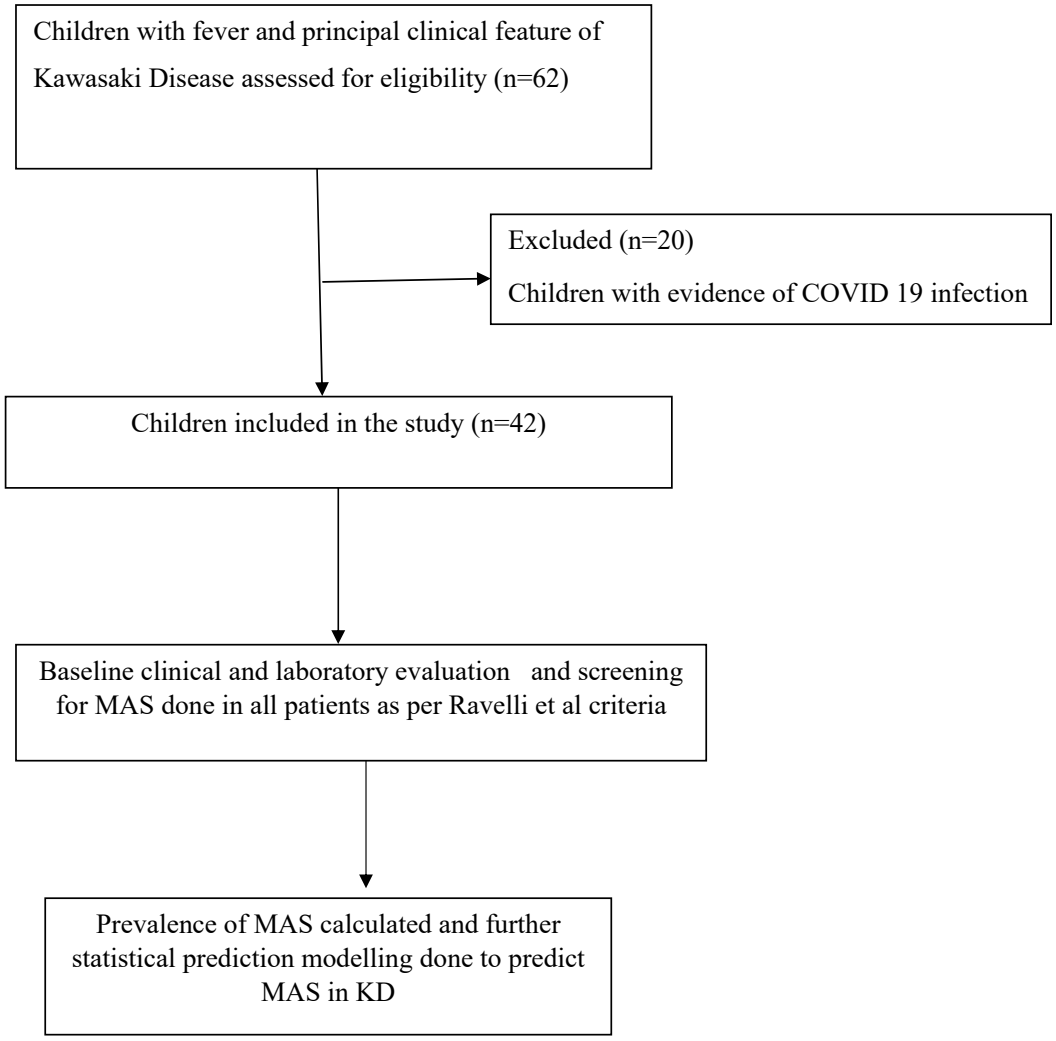

Fig. 1 Study flow chart depicting enrolment and follow-up of participants

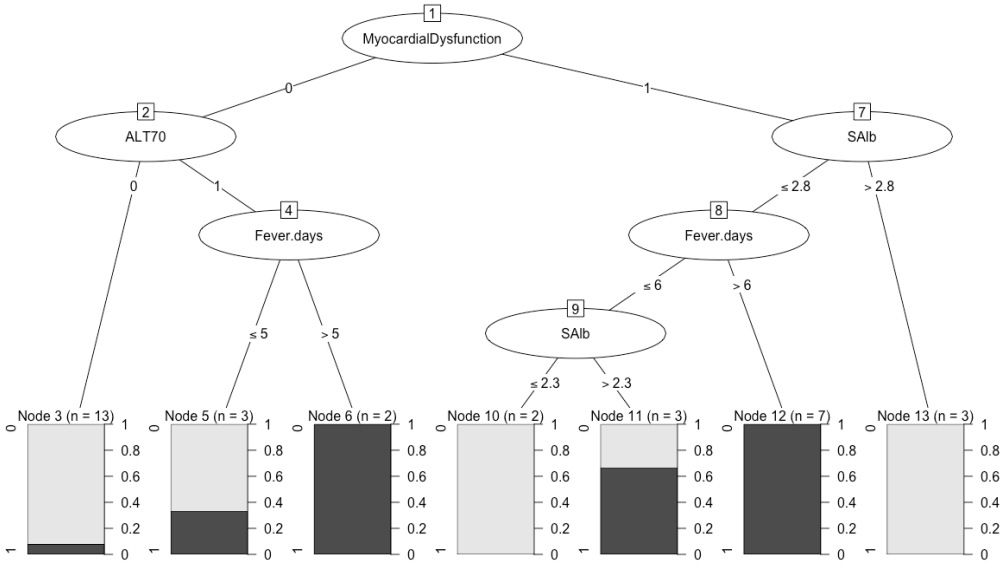

Fig. 2. Classification tree predicting macrophage activation syndrome in Kawasaki disease in children

Note: Terminal nodes 3, 5, 6, 10, 11, 12 and 13 depict the proportions of patients with and without MAS. Terminal nodes 6 and 12 included only patients with MAS.

**ALT > 70 (0 No, 1 Yes)*

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Profile of Children with Kawasaki Disease Associated with Tropical Infections

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Abstract

Objective To describe various infectious triggers for Kawasaki disease (KD) in India.

Methods A series of 10 children with diagnosed infections who developed KD during their course of illness has been presented. They were diagnosed by the American Heart Association (AHA) 2017 guidelines. Echocardiography was done to check for coronary artery dilation. Treatment was instituted as per standard protocol.

Results Kawasaki disease was diagnosed in 8 boys and 2 girls, aged 1 mo to 11 y. These children were being treated for dengue, chikungunya, SARS-CoV-2, hepatitis A, tuberculosis, brucellosis, disseminated staphylococcal sepsis, scrub typhus, and enteric fever.

Conclusions Kawasaki disease has been associated with infectious triggers. It should be considered in febrile patients with mucocutaneous involvement or in nonresponsive sepsis, despite adequate therapy.

Keywords Coronary artery aneurysm · Infection · Kawasaki disease

Introduction

Kawasaki disease (KD), originally called 'mucocutaneous lymph node syndrome' is the most common vasculitis of childhood. The diagnosis is mainly clinical based on American Heart Association (AHA) 2017 criteria [1]. There are no pathognomic laboratory tests that can be used to confirm the diagnosis. It is often missed because the clinical features of KD overlap with common childhood infections like measles, dengue, scarlet fever, parvovirus B19, and other viral exanthems. The etiology is still unknown, though multiple theories have been proposed based on available epidemiological data [2]. The current consensus is that an infectious trigger initiates an abnormal and robust innate inflammatory response in genetically predisposed children [3].

The most frequent association of KD is with viral infections like Epstein–Barr virus, cytomegalovirus, adenovirus, parvovirus B19, herpes virus 6, parainfluenza type 3, measles, rotavirus, dengue virus, human immunodeficiency virus, varicella, H1N1 2009 pandemic influenza, coronaviruses, and coxsackie B3 virus [4–19]. Even bacteria like *Staphylococcus aureus* and Streptococcus pyogenes have been implicated [20]. Most of these studies are from *U.S.A., China, Korea, Taiwan, and Australia* [21]. There is lack of literature from India regarding the profile of KD associated with infections. A series of 10 cases with an infection associated KD is reported in this paper.

Material and Methods

This was a single-center prospective case review of children who were initially admitted with acute febrile illness of infectious etiology. These children were diagnosed to have an infection based on clinical and laboratory findings. They did not show improvement or deteriorated despite adequate antibiotic and supportive therapy. On further investigation, they were diagnosed as KD according to AHA 2017 criteria [1]. Patients with fever, who fulfill 4 of the 5 principal clinical features are said to have classical/complete Kawasaki disease. Those who meet less than 4 criteria are classified as incomplete Kawasaki disease. All such patients admitted

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between January 2019 and January 2021 were included. The demographic profile, anthropometry, clinical features, laboratory findings (complete blood count, liver function tests, kidney function tests, ESR, CRP, ferritin, fibrinogen, D-dimer), echocardiographic findings, and treatment details were collected from case records and entered in a prestructured proforma. Informed consent from patient caregiver and permission from Institution ethics committee was obtained.

Data entry was done in Microsoft excel sheet and analyzed. Measures of central tendency to find mean and median were used. R software was used for statistical analysis.

Table 1 Demographic and clinical profile of the children with infection-associated KD

Patient characteristics (number)	*N* = 10
Age (months, median; IQR)	57; 24–108
Gender (male:female)	8:2
Duration of fever [days, (median; IQR)]	5; 5–6
Rash (number of patients, %)	4; 40
Mucositis (number of patients, %)	8; 80
Lymphadenopathy (number of patients, %)	3; 30
Eye redness (number of patients, %)	9; 90
Desquamation of the skin (number of patients, %)	8; 80
Extremity edema (number of patients, %)	8; 80
Infectious etiology	*N* = 10
Staphylococcus aureus	2
Rickettsial (scrub typhus)	1
Brucella + tuberculosis	1
Dengue + chikungunya + staphylococcus (coinfection)	1
Hepatitis A	1
COVID-19 (RT-PCR+)	1
Pseudomonas	1
Typhoid	1
Dengue	1

COVID-19 Coronavirus disease 2019; *IQR* Interquartile range; *KD* Kawasaki disease; *RT-PCR* Reverse-transcription polymerase chain reaction

Result

Ten patients were enrolled in the study. The baseline demographic, clinical details, and associated infections are shown in Table 1 and 2. Six cases (60%) with infections responded to antimicrobials and their fever resolved. They subsequently had fever with principal clinical findings and echocardiography, that was suggestive of KD. Four patients (40%) had persistent fever despite appropriate antimicrobial initiation, with new onset principal clinical findings of KD. This was confirmed by echocardiography. The median duration of recurrence of fever or new onset principal clinical findings with fever was 5 d. The median age of the patients was 57 mo (IQR 24, 108). The disease was 4 times more common in boys. The presenting complaints included fever, rash, extremity edema, and mucositis with cracking and fissuring of lips.

Complete and incomplete KD were seen in 5 children each. There were no atypical cases showing central nervous system, renal, or musculoskeletal system involvement [22]. The spectrum included both viral and bacterial infections as shown in Table 2. One of the cases was diagnosed to have bacterial and viral coinfection based on blood culture showing methicillin-resistant *Staphylococcus aureus* (MRSA) along with NS1 antigen (nonstructural protein 1) positive for dengue. He was also found to have IgM positive

Table 2 Clinical profile of patients

Etiology	Fever	Oral mucositis	Conjunctivitis	Rash	Edema/Desquamation	Lymphad-enopathy	ESR/CRP ↑	Echocardiogram
Staphylococcus	+	−	+	+	+	+	+	+
COVID-19	+	+	+	+	+	−	+	+
Staphylococcus + dengue + chikungunya	+	+	+	−	+	−	+	+
Dengue	+	+	−	+	+	−	+	+
Brucella	+	+	+	−	+	+	+	+
Scrub typhus	+	+	+	+	+	−	+	+
Staphylococcus	+	+	+	−	−	−	+	−
Hepatitis A	+	−	+	−	+	−	+	+
Pseudomonas	+	+	+	−	−	−	+	+
Enteric fever	+	+	+	−	+	+	+	−

COVID-19 Coronavirus disease 2019; *CRP* C-reactive protein; *ESR* Erythrocyte sedimentation rate

+ indicates presence and − indicates absence of a clinical feature

for chikungunya. The laboratory investigations have been depicted in Table 3. The CRP and ESR values were raised over AHA defined cutoff of over 3 mg/dL and 30 mm/h, respectively in all the patients. The echocardiography findings at diagnosis and follow-up of the patients have been described in Table 4. Eight children (80%) with KD had abnormal echocardiography findings at diagnosis. Four children had coronary artery aneurysms (CAA) at diagnosis as indicated by z scores of ≥ 2.5. Two children had coronary dilatation with coronary *z* scores of 2–2.5. Two others had normal coronary *z* scores at diagnosis but showed a decrease of ≥ 1 SD score at follow-up and were classified as coronary dilatation as per AHA 2017 guidelines [1]. One of the patients showed periarterial enhancement and lack of tapering at the time of diagnosis. Another child had normal echocardiography and 4 principal clinical findings of KD. Out of these 8 children, 2 had persistent CAA on follow-up and remaining showed normalization of echocardiographic findings on follow-up.

All patients received IVIG and aspirin at diagnosis. Eight (80%) children responded to first dose of IVIG and aspirin. Two patients required additional therapy like second dose of IVIG, steroids, and infliximab. Case 5 needed infliximab infusion. Both IVIG-resistant patients had CAA

Table 3 Laboratory indices of children with infection-associated KD

Parameter	Median (IQR)
Hemoglobin (g/dL) (median, IQR)	9.1 (7.9–10.2)
Total lymphocyte count (thousand/mm^3) (median, IQR)	13.25 (10.10–23.40)
Absolute neutrophil count (thousand/mm^3) (median, IQR)	7.31 (6.7–18.2)
Platelets (lacs/mm^3) (median, IQR)	3.11 (1.9–4.8)
ESR (mm/first hour) (median, IQR)	31.5 (28–37)[a]
CRP (mg/dL) (median, IQR)	73 (43–109)[a]
D-dimer (ng/mL) (median, IQR)	693 (323–990)
Fibrinogen (mg/dL) (median, IQR)	217.5 (181.2–299.5)
Ferritin (ng/mL) (median, IQR)	415.5 (267.5–745.2)
AST (IU/L) (median, IQR)	43.5 (29–97)
ALT (IU/L) (median, IQR)	54 (25–178)
Albumin (g/dL) (median, IQR)	2.9 (2.3–3.1)
Triglycerides (mg/dL) (median, IQR)	165 (133–214)
Urea (mg/dL) (median, IQR)	26 (19–48)
Creatinine (mg/dL) (median, IQR)	0.35 (0.2–0.5)

CRP C-reactive protein; *ESR* Erythrocyte sedimentation rate; *IQR* Interquartile range; *KD* Kawasaki disease

[a]indicates raised median values

Table 4 Echocardiography coronary artery *z* scores at admission and follow-up

Case no	Coronary artery *z* score at admission			Coronary artery *z* score at 1 mo follow-up		
	LAD	RCA	LMCA	LAD	RCA	LMCA
1	−0.06	−0.11	+1.35	−0.96	−1.38[b]	−0.07[b]
2	+1.32	+2.0	+1.02	+0.04[b]	+0.3[b]	+0.16
3	+1.13	+3.67[a]	+2.36	−0.72	+1.75	−1.12
4	+1.84	+1.04	+2.34	−0.79[b]	+0.03[b]	−1.09[b]
5	+3.06[a]	+3.07[a]	+3.84[a]	+2.7	+1.9	+3.1
6	+3.2[a]	+1.53	+1.54	−0.07	+1.28	−1.17
7	+1.56	+0.40	+1.42	+1.5	+0.4	+1.4
8	+1.34	+0.32	+1.8	+0.42	+0.10	−0.19[b]
9	+2.7	+3.5[a]	+1.5	+3.07	+2.08	+1.28
10	+0.14	+0.52	+0.18	+0.29	+0.61	+0.06

LAD Left anterior descending artery; *LMCA* Left main circumflex artery; *RCA* Right coronary artery

[a]Coronary artery aneurysm (*z* score > 2)

[b]dilated coronary artery; > 1 *z* score decrease following treatment

that regressed following second-line therapy. In the present series, no child had myocarditis, Kawasaki disease shock syndrome (KDSS), or macrophage activation syndrome (MAS). None of the patients required vasopressors, ventilator support, or anticoagulants.

Discussion

The paradigm of KD has changed in the setting of SARS-CoV-2 pandemic in recent times [23, 24]. It has come back in focus with emergence of multiple reports of pediatric multisystem inflammatory disease (PMIS) or multisystem inflammatory syndrome in children (MIS-C) with KD-like features often complicated with myocarditis, shock, and MAS [25]. The AHA 2017 guidelines have simplified the approach, diagnosis, and treatment of KD in children. It has also emphasized the occurrence of KD associated with preexisting infections. It is mainly described in context of multiple known viral infections [26]. In the present series, various infectious triggers for KD in India are described. These included different bacteria like MRSA, brucella, salmonella, pseudomonas, and rickettsia and viruses such as the SARS-CoV-2, dengue, chikungunya virus, and hepatitis A. It is well known that these infections are endemic to the Indian subcontinent, but there is scarcity of literature from India that shows association of KD in presence of these tropical infections.

In the patients included in the study, the clinical features included 5–6 d of fever with conjunctival injection, rash, and mucositis with cracking and fissuring of lips. Children with febrile illnesses are often treated with antibiotics. There is a common clinical practice to upgrade antibiotics if fever does not subside. The possibility of KD in such patients must be considered, especially in presence of subtle signs like skin rash or extremity edema, cracking of lips, strawberry tongue, conjunctivitis, and lymphadenopathy. These signs are often attributed to drug allergies/reactions, poor hygiene, micronutrient deficiencies or the underlying infection. The alternative line of treatment (IVIG, aspirin or steroids) can then be considered, thereby preventing antibiotic misuse and coexisting emergence of resistance [27].

The values of ESR and CRP were raised above the AHA-defined cutoff for diagnosis of KD in all children included in the study. Literature review shows that the ESR is elevated during acute phase but is an unreliable marker following IVIG administration. CRP is another nonspecific marker that correlates with the risk of CAA. Inflammatory biomarkers such as procalcitonin, total leucocyte count, mean platelet volume, platelet distribution width, peripheral blood eosinophilia are nonspecific and of limited clinical use [28]. N-terminal pro b-type natriuretic peptide (NT-pro-BNP) is a cardioselective biomarker useful for diagnosis of KD, although its values vary with age. Prospective pediatric studies evaluating the role of NT-pro-BNP in the diagnosis of KD recommend cutoff values of between 190 ng/L and 260 ng/L [29]. In children where there is high suspicion of KD, this may be used as an adjunct to the clinical and echocardiography findings.

In the present study, 4 (40%) children had CAA and 4 (40%) had dilated coronary arteries as per AHA-2017 criteria. This is higher than the overall incidence of CAA in KD, i.e., 15–20% [1]. A possible reason for this could be that pre-existing infections can also contribute to coronary dilation [30, 31] or time spent awaiting antimicrobial response in a febrile patient or multiple consultations sought by parents before diagnosis is made. Reyna et al. showed coronary artery dilatation in 26% of non-Kawasaki febrile viral exanthematous illnesses. They have explained this phenomenon by compensatory increase in coronary artery blood flow to meet the myocardial oxygen demand in fever and tachycardia [30]. In a study done by Chbeir et al., cardiac abnormalities were noted in an initial echocardiogram in 31% of patients and in 11% of the echocardiograms performed at 6 wk after disease onset. They have explained this higher involvement by including any abnormal echocardiographic findings, in particular perivascular brightness of the coronary arteries [32]. The authors hypothesize that infections in a genetically predisposed child lead to hyper-responsiveness of the innate immune pathway. The accompanying inflammation and cytokine stormcontributes to increased incidence ofcoronary artery involvement.

Management of KD consists of IVIG infusion at a dose of 2 g/kg given over 12 h and 80–100 mg/kg aspirin. In children with myocarditis the infusion may be given over 18–24 h to avoid fluid overload. In case of varicella- or influenza-triggered KD, high-dose aspirin should not be given. It can be followed with an alternative antiplatelet agent (clopidogrel), once afebrile or low-dose aspirin as it does not pose the risk of Reyes syndrome [1]. Persistence of fever beyond 36 h after completion of IVIG indicates IVIG resistance and warrants treatment with second line therapies. There might be clinical confusion regarding the need for second-line therapy for KD due to coexisting infection. The authors suggest that echocardiography along with NT-pro-BNP levels may help guide therapy in that case. In presence of CAA/coronary artery dilatation it may be prudent to give a second dose of IVIG with or without steroids. Only 2 patients in the present study needed second-line therapy including infliximab. Though further research is needed to make a universal recommendation. The patient with dengue, in the present study, had an improving platelet count when KD was considered and aspirin was initiated once platelets were over 1,00,000/mm^3.

This study is the first of its kind to show the spectrum of infections that can lead to KD in a tropical country like

India. In the present series no child had myocarditis, KDSS, or MAS. Early identification of KD in these cases and prompt appropriate therapy may prevent long-term cardiac complications [33]. However, the limitation of the study is that the sample size is small and it has been conducted over a short time period.

Conclusion

In the present series of 10 children who developed KD in the course of their infectious illness, the clinical presentation included fever with conjunctival injection, rash and mucositis with cracking and fissuring of lips emerging as the most common signs. Most of the patients showed echocardiographic abnormalities but responded favorably to IVIG. This highlights that the presence of a pre-existing infection does not rule out the possibility of KD. The signs are often subtle and may be missed or attributed to drug allergies/reaction, poor hygiene, and micronutrient deficiencies or the underlying infection. Antibiotics are upgraded in these scenarios leading to unnecessary antibiotic usage and emergence of resistance. Increased awareness would help in early diagnosis, prompt treatment, and preventions of long-term cardiac complications. Easily available biomarkers like NT-pro-BNP may help in cases where clinical and echocardiography findings are inconclusive.

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Authors' Contributions AM, DM, VK, and AM conceptualized the idea, drafted the manuscript, and managed the patients; SY helped in collection and analysis of the data; AR, KD, HM, and SS helped in management of the patients. VK will act as the guarantor for this paper.

Declarations

Conflict of Interest None.

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Clinical Review

OXFORD

CLINICAL REVIEW

Kawasaki Disease with Peripheral Gangrene in Children: A Case Series and Review of Literature

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ABSTRACT

Kawasaki disease (KD) is a medium vessel vasculitis of childhood particularly affecting the coronary arteries and leads to aneurysms in 15–25% of untreated patients. It is a rare cause of peripheral limb gangrene in children under 5 years. Most of the cases in literature are reported during infancy. The median age of KD in patients with gangrene is 3 months and the median time for onset of signs of ischaemic necrosis is 2–4 weeks after the diagnosis and often leads to amputation of the affected limb. Even with early treatment, salvaging the limb is difficult and often not successful. There is an acute risk of mortality and long-term morbidity if the underlying inflammatory process is not identified and treated in a timely manner. We present four cases of KD, who had peripheral limb gangrene at the time of presentation. Initial workup for infective aetiology and pro-coagulant state were negative. Diagnosis of peripheral limb gangrene secondary to atypical KD was made on the basis of echocardiography and laboratory findings.

KEYWORDS: biologicals, IVIG, Kawasaki disease, peripheral gangrene

INTRODUCTION

Kawasaki disease (KD) is the most common vasculitis of childhood especially in Southeast Asia region. It is a medium vessel vasculitis, commonly affecting young infants and children below 5 years of age. Most common vessels involved are coronary arteries; however, other arteries like coeliac, mesenteric, femoral, iliac, renal, axillary and brachial arteries may also be affected [1]. The pathogenesis involves immunoglobulin A (IgA) mediated inflammation and fibrinoid necrosis of vessel wall. Histopathological studies indicate that multiple organs and tissues are involved, but long-term sequelae seem to occur only in coronary arteries [2].The macrophages play an

important role in the initial phase unlike many other vasculitis syndromes suggesting innate immune hyperactivity. These destructive processes are not limited to coronary arteries and can occur in other vessels too leading to vascular insufficiency and end organ damage.

Peripheral gangrene is a rare complication of KD, reported mainly in infants. The time for onset of gangrene is usually 2–4 weeks after the diagnosis of KD [3]. We are reporting four cases of infants with KD and gangrene at the outset. Very high index of suspicion is needed for diagnosis of KD in infants and young children presenting with peripheral gangrene with or without fever. Early treatment of these cases with intravenous immunoglobulin (IVIG), steroids and aspirin will prevent limb loss. The prognosis of peripheral gangrene in patients with KD remains guarded and many children need amputation of limbs [4].Thus there is a need to have separate set of diagnostic criteria encompassing peripheral gangrene and other atypical manifestations of KD in infancy. Even in older kids, gangrene and Takayasu-like presentation in children <10 years, KD should be considered as it is easily amenable to therapy with good outcomes if treated within therapeutic window.

CASE 1

A 14-month old boy presented with fever and dry gangrene of bilateral feet since 10 days (Fig. 1A). He also had history of eye redness and cracking of lips. In addition, there was extensive perineal and periungual desquamation. On examination, vitals were stable. Mild pallor was present. Anthropometric parameters were normal. Bilateral lower limbs had dark bluish discolouration involving all toes and extending till ankle region. Dorsalis pedis pulse was not palpable bilaterally. Rest systemic examination was within normal limits. Initial laboratory investigation showed haemoglobin (Hb) of 8.4 g/dl, total leukocyte count (TLC) was 24 900/mm^3 (60% neutrophils) and platelets were 1.09×10^5/mm^3. Coagulation profile was normal with international normalized ratio (INR) of 1.05 with D-dimer of 2490 ng/ml. Inflammatory markers were raised with C reactive protein (CRP) of 111 mg/l and erythrocyte sedimentation rate (ESR) of 49 mm. Blood and urine cultures were sterile. Swab from the gangrene margin was sterile. Chest X-ray and Doppler of the lower limbs were normal. In view of fever and two principal features (i.e. desquamation and history of eye redness), KD with peripheral arterial disease leading to gangrene was suspected. Echocardiography (ECHO) was suggestive of coronary artery dilatation which confirmed our diagnosis. The left main coronary artery (LMCA) standard deviation (SD) score was +1.89, left anterior descending (LAD) SD score +2.28, right coronary artery (RCA) SD score was +1.56 and there was lack of tapering of these vessels. This was classified as coronary artery dilatation of LAD. In view of established gangrene, magnetic resonance (MR) angiography was done for aorta and its branches which revealed narrowing of lower limb arteries (Fig. 1B). Procoagulant states workup, i.e. anti-phospholipid antibody (APLA), homocysteine levels, protein C, protein S were in normal range. After 1 month follow up, reduction of LMCA SD score to +0.77 was confirmatory of coronary artery dilatation of LMCA as well. He was treated with two doses of IVIG, aspirin, low molecular weight heparin (LMWH) and methylprednisolone pulse. Amputation was done for the gangrenous limb on follow up.

CASE 2

A 6-month boy presented with complaints of fever for 10 days, swelling of his left hand with bluish discolouration and painful movements of all fingers. There was no preceding history of vomiting, loose motion, rash, eye redness, skin changes or trauma. On examination, child was hemodynamically stable. Distal pulse was weak in left hand. There was gangrene of finger tips of left hand with no line of demarcation with bluish discolouration of palm, dorsum of hand and 3–4 cm of distal forearm. Hb was 11.6 g/dl, TLC of 16 400/mm^3 (85% neutrophils) and platelet count of 6.2×10^5/mm^3. The ESR was 32 mm in first hour and CRP of 62 mg/l. Serum procalcitonin was less than 0.5 ng/ml. The glutamic-oxalacetic transaminase (SGOT) and glutamic-pyruvic transaminase (SGPT) were 100 and 67 IU/L, respectively. Renal function tests were normal. Serum albumin was 2.5 g/dl and sodium was 129 mEq/L. Urine routine showed 25 pus cells/hpf. Both urine and blood cultures were sterile. The INR

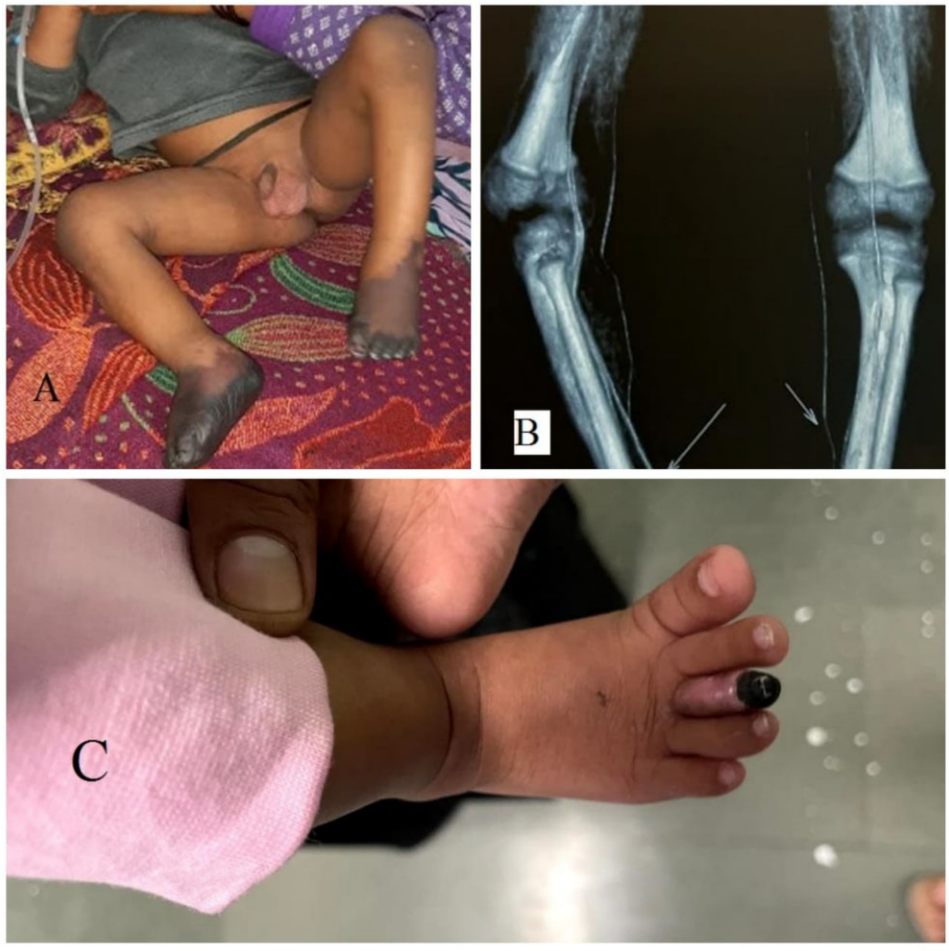

Fig. 1. (**a**) Gangrene involving feet (case 1); (**B**) MR angiogram showing narrowing of lower limb arteries (case 1); (**C**) Early gangrenous changes in foot (case 3).

was normal with borderline raised D-dimer of 276 ng/dl. Doppler showed decreased peak systolic velocity (PSV) in distal radial and ulnar arteries of left hand with no evidence of thrombus.

KD was suspected based on history of fever without a focus in an infant with no discernible cause and supportive laboratory findings indicative of incomplete KD. An ECHO was planned which showed SD score of +0.45 in LMCA, +1.27 in LAD and +0.34 in RCA. The child was treated with two doses of IVIG and pulse methyl prednisolone, LMWH and aspirin on follow up. Fever responded to the second dose of IVIG but gangrene progressed proximally. We administered infliximab following which the gangrene halted. The workup for pro-coagulant states, i.e. APLA, homocysteine levels, protein C, protein S, vitamin B12 and folic acid were in normal range. On follow up ECHO, there was >Δ1 change in LMCA SD score confirming the diagnosis of KD and coronary artery dilatation of LMCA with peripheral arterial disease.

CASE 3

A 2-month old male infant presented with complaints of fever and irritability for 7 days. At admission, child had mild pallor along with left lower limb gangrene involving the fourth toe (Fig. 1C). The rest of the systemic examination was normal. On examination, bilateral lower limbs had bluish

discolouration and gangrene of fourth toe. He was treated for suspected sepsis with broad spectrum antibiotics and IV fluids. Investigations showed haemoglobin of 7.5 g/dl, leucocytosis with TLC of 26 000/mm^3 (84% neutrophils) and platelet count of 7.53×10^5/mm [3]. Inflammatory markers were raised with CRP of 172 mg/dl but procalcitonin was <0.5 ng/ml. Serum albumin was 2.8 gm/dl. Liver function test were mildly elevated with SGOT and SGPT of 57and 53 IU/L, respectively. Renal function tests and urinalysis was normal. Cultures showed no growth. Coagulation profile and D-dimer were normal while fibrinogen and ferritin were elevated to 503 mg/dl and 1037 ng/dl, respectively.

Doppler study of both lower limbs was unremarkable. Echocardiography showed SD score of 0.55 in LMCA, 1.84 in LAD and 0.07 in RCA. The baby was diagnosed as incomplete KD based on clinical and laboratory criteria as per American Heart Association (AHA) 2017 guidelines. The ECHO on follow up showed >Δ1 change in SD score of LAD (SD 0.04). Thus confirming the diagnosis of incomplete KD with coronary artery dilatation of LAD. After treating with IVIG, aspirin and pulse methylprednisolone, the gangrene halted and only involved a part of fourth toe. On follow up, workup for protein C and S was normal.

CASE 4

A 2-month old girl child with uneventful birth and neonatal period, presented with fever, loose stools and vomiting for 5 days. On examination, there was mild pallor and bluish discolouration of finger tips of left hand and toes of lower limbs. The child was treated with intravenous fluids and broad spectrum antibiotics were started. Despite antibiotics and fluid resuscitation, the child continued to have persistent tachycardia along with tachypnoea, but blood pressure was normal for age. The N-terminal pro b-type natriuretic peptide (NT-proBNP) was 21 000 pg/ml, which was markedly raised along with raised creatinine phosphokinase (CPK-MB) of 230 U/L. Preliminary investigations showed Hb of 10.9 g/dl, TLC of 27 110/mm^3 (75% neutrophils), platelet count of 0.8×10^5/mm^3. The CRP was 48 mg/L. Serum albumin was 2.2 gm/dl. Liver enzymes were mildly raised with SGOT and SGPT of 145 and 58 IU/L, respectively. Renal function tests were normal. Venous blood gas showed high anion gap acidosis with raised lactate, which normalized within 24 h of treatment. Urine routine examination revealed >25 WBC/hpf and culture was sterile. SARS-CoV-2 serology was negative. Bluish discolouration of toes of feet and left forearm worsened with gangrenous changes and necrotic patch on right arm. Dorsalis pedis was not palpable bilaterally. Coagulation profile was normal, fibrinogen was very low (64 mg/dl) and D-dimer was raised eight times the upper limit of normal. Diagnosis of Incomplete Kawasaki Disease shock syndrome (KDSS) was made as per AHA 2017 criteria and IVIG was given. ECHO showed mild tricuspid regurgitation. The SD scores of LAD, LMCA and RCA were +1.2, +1.04 and +0.96, respectively. With therapy shock improved and gangrene started improving after methyl prednisolone pulse. Pro-coagulant workup was negative. Enoxaparin was started and later on switched to aspirin. Child was discharged with minimal gangrene. On follow up, the ECHO revealed >Δ1 change in SD score of LAD. The child only had residual gangrene of fourth toe.

DISCUSSION

KD in infants often poses a diagnostic challenge to the treating physicians, as almost 88% cases are of incomplete phenotype and are often associated with atypical presentations like peripheral gangrene, CNS abnormalities, ophthalmological and musculoskeletal problems. Even AHA 2017 guidelines lay special emphasis on diagnosis of KD in infants. Most of these cases are diagnosed late beyond 10 days of illness, leading to loss of ideal window for IVIG administration for optimal outcome. All the cases described in our series had incomplete KD phenotype and had coronary artery dilatation, though initial ECHO findings except for the case 1 were normal. Follow up studies showed >Δ1 change in SD score of coronary artery diameter indicating dilatation as per AHA 2017 criteria. None of the cases had residual coronary artery aneurysm. Moreover, the principal clinical

features of KD like rash, mucositis, eye redness, extremity oedema and lymphadenopathy were absent in three of our cases. Thus, in infancy even in the absence of principal clinical features, KD should be suspected in cases presenting with gangrene [2].

Peripheral gangrene is an uncommon finding in paediatric clinical practice. Most common causes of peripheral gangrene in this age group is disseminated intravascular coagulation (DIC) secondary to gram negative or gram positive bacterial sepsis [5]. In all our cases, the blood, urine and other cultures were sterile. The procalcitonin levels done in three of our cases were not indicative of bacterial sepsis. Other notable causes include severe dehydration secondary to gastroenteritis, measles, hyperleukocytosis secondary to haematological malignancy, cardiac defects like tricuspid atresia/shunt failure secondary to embolic phenomenon. Peripheral gangrene is observed in Takayasu arteritis and polyarterits nodosa also but their usual age of presentation is late childhood and early adolescence [6, 7]. The vasculitic involvement of brachial, popliteal, anterior and posterior tibial artery in KD can manifest as limb gangrene in children. This phenomenon is more commonly reported in children <5 years of age. Al Tasseh *et al.* [3] have reported the median age of KD with gangrene to be 3 months and the median time for onset of signs of ischaemic necrosis to be 2–4 weeks after diagnosis of KD. All four of our cases were under 2 years of age and they had gangrene as a presenting feature. Al Tasseh *et al.* [3] reported a 14-month child with KD with peripheral gangrene and Factor V laden mutation. Inherited thrombophilia workup was negative for all our cases. In a study by Ahluwalia *et al.* [8] in North India, it was determined that factor Leiden mutation, protein C, S and anti-thrombin III deficiency were not common in paediatric cases with peripheral gangrene .This was similar to our series where we did not find any underlying inherited pro-coagulant state.

There are a wide range of medications which have been used in management of KD with gangrene like IVIG, heparin (unfractionated or low molecular weight), steroids, hydralazine, propranolol, warfarin, urokinase, prostacycline, dipyridamole, nitroprusside, tissue plasminogen activator, cyclophosphamide, glyceryl trinitrate, nifedipin and even caudal block [9]. In the literature reviewed, most commonly used therapy was IVIG that had been used in all of the cases while steroids were given in 20 out of 23 cases (Table 1). We used IVIG, methylprednisolone, aspirin and enoxaparin in our patients. In case 2, gangrene was progressive despite two doses of IVIG and methylprednisolone pulse, so infliximab was added. Most of these cases present like sepsis, and often echocardiography initially is normal. Therefore, in presence of sepsis like illness with gangrene, it may be prudent not to delay IVIG treatment in infants, as the benefit of early administration far exceeds withholding treatment till diagnosis is made. In countries where there is high risk of infection, IVIG along with broad spectrum antibiotics maybe crucial for decreasing morbidity and mortality. Amputation of the affected part is a known complication of gangrene in KD. Among reviewed cases, most experienced either autoamputation or surgical amputation was required. Amputation was done in two of four cases reported in present study. Most of our cases were pre-pandemic and case 4 was during SARS-CoV-2 pandemic. In cases 3 and 4, early treatment before established gangrene led to a favourable outcome in comparison to cases 1 and 2.

CONCLUSION

We conclude that peripheral gangrene in infancy and early childhood age group should be considered as a manifestation of KD. Even in the absence of principal clinical criteria one must evaluate for KD with an echocardiography and biochemical parameters as per AHA 2017 guidelines along with NT-proBNP. We also suggest that presence of peripheral gangrene in children less than 5 years may be included in the diagnostic criteria or a standalone criterion for diagnosis of KD. This is especially important in infants and children <5 years of age. Prompt use of IVIG in addition to steroids and LMWH may be lifesaving in children.

Table 1. Summary of cases with Kawasaki disease and peripheral gangrene

Study	Age	Sex	Gangrene/blood vessel involved	Anti-inflammatory therapy	Anti-thrombotic/ thrombolytic therapy	Outcome	Follow up status
Tomita *et al.* [10]	2 months	Female	• Cyanosis of both hands • Coronary vessels, axillary artery	IVIG	Heparin TPA Urokinase PGE1 TNG	Autoamputation of distal part of left fourth and fifth fingers	61 day follow up showed giant aneurysm of coronary and axillary arteries
	2 months	Male	• Gangrene of distal phalynx of left third finger • Coronary, Brachial and subclavian arteries	IVIG	Heparin Coumadin	Autoamputation of gangrenous part	2 year follow up showed multiple small aneurysms in LCA and giant aneurysm in RCA
	3 months	Female	• Gangrene of right foot, left hand and left lower leg and foot • Coronary, internal mammary and axillary arteries	IVIG Methyl pred	Heparin Dipyridamole	Autoamputation of gangrenous part	61 day follow up showed no progression in coronary dilatation
Von Planta *et al.* [11] 1995	2 months	Female	• Left hand and feet • Multiple aneurysms of left coronary artery and giant aneurysm of left anterior descending artery	IVIG	PGE1 Aspirin Lidocain Heparin Iloprost (prostacyclin analogue)	Gangrene resolved without much sequalae	Multiple coronary artery aneurysms at discharge
Chang *et al.* 1999 [12]	8.5 months	Male	• Patches of ischaemia over feet, palms, and distal digits	IVIG	Aspirin Heparin Dipyridamloe	Amputation of distal phalynx of right middle finger	After 9 months, dilatation of RCA decreased

(continued)

Table 1. (continued)

Study	Age	Sex	Gangrene/blood vessel involved	Anti-inflammatory therapy	Anti-thrombotic/ thrombolytic therapy	Outcome	Follow up status
			• Dilatation of both right and left coronary arteries				
Brenner *et al.* 2000[13]	3 months	No mention	• Peripheral gangrene • Multiple cardiac and extra cardiac aneurysms and thrombus	No mention	No mention	Death	–
	5 months	No mention	• Peripheral gangrene	IVIG steroids	Acetylsalicylic acid	Death	–
Krohn C *et al* 2001[14]	3 months	Female	• Gangrene of left forehand and left forefoot • Intestinal stenosis and coronary aneurysms	IVIG Systemic steroids	Salicylates rTPA LMWH	Bowel resection and amputation of affected part	Thrombosis resolved, no signs of myocardial damage persisted
Durall *et al.* 2006[15]	5 weeks	Male	• Bluish discolouration of hands and feet • Dilated coronary arteries	IVIG Methyl pred Second dose IVIG	Aspirin Heparin infusion Anti-thrombin III TNG patch Dipyridamole Abciximab (short infusion)	Autoamputation of gangrenous part	Echo normal on follow up
Dogan *et al.* 2007[16]	–	–	• Gangrene of feet • Coronary aneurysms	IVIG Methyl pred	Aspirin Heparin Prostacyclin analogue	Resolved	

(continued)

Table 1. (continued)

Study	Age	Sex	Gangrene/blood vessel involved	Anti-inflammatory therapy	Anti-thrombotic/ thrombolytic therapy	Outcome	Follow up status
O'Connor *et al.* 2007 [17]	2 months	Male	• Bluish discolouration of left foot • Giant aneurysms of right coronary artery and fusiform aneurysms of left coronary artery	IVIG Methyl pred Infliximab	Heparin, Topical nitroglycerine	Small areas of gangrene were present in four toes	Follow up at 1 year of age showed persistence but decrease in size of aneurysms
Kim *et al.* 2008[18]	2 months	Male	• Tips of distal phalynx of fingers and toes • Saccular aneurysms of right coronary and left anterior descending arteries	IVIG (two doses) Dexamethasone Methotrexate	Aspirin Heparin Dipyridamole Warfarin	Ischemic regions completely resolved	Follow up after 1 year showed fusiform aneurysmal dilatation of both coronary arteries, iliac bifurcation and axillary arteries
Gomez-Moyano *et al.* [19]	4 months	Male	• Three aneurysms in coronary arteries • Gangrene of fingers and toes	IVIG Methyl pred	Heparin, Aspirin PGE1, intravenous nitroglycerine, dipyridamole	Surgical Amputation of gangrenous part	Suffered myocardial infarction during hospitalization No issues at 1 year follow
Varma *et al.* [4]	1 year	Male	• Gangrene of toes and fingers • No comment on coronary vessels	No mention	Aspirin	Autoamputation	No comment

(continued)

Table 1. (continued)

Study	Age	Sex	Gangrene/blood vessel involved	Anti-inflammatory therapy	Anti-thrombotic/ thrombolytic therapy	Outcome	Follow up status
Malekzadeh *et al.* [9]	4 months	Male	• Multiple aneurysms in all coronary arteries, both subclavian, external and internal iliac, bronchial, renal and mesenteric arteries • Gangrene of toes of both lower limb and right upper limb	IVIG Methyl pred Cylophosphamide	Aspirin Heparin	Autoamputation of gangrenous part	1 year follow up: very mild improvement in coronary aneurysms Peripheral aneurysms persisted
	6 months	Female	• Descending aorta dilatation (known case of PHACE syndrome) • Gangrene of finger of right hand	IVIG Methyl pred	Aspirin	Peripheral cyanosis and gangrene improved	6 month follow up: coronary dilatation improved comparatively
	1 year	Male	• Peripheral gangrene of distal phalynx • Multiple aneurysms in RCA, LMCA, LAD	IVIG Methyl pred Azathioprine (3 months) Second pulse IVIG+methylpred Infliximab	Aspirin Warfarin Heparin	Gangrene improved in size	Initially size of aneurysms decreased but on 2 month follow up no recovery in coronary aneurysms

(continued)

Table 1. (continued)

Study	Age	Sex	Gangrene/blood vessel involved	Anti-inflammatory therapy	Anti-thrombotic/ thrombolytic therapy	Outcome	Follow up status
Krishnamurthy *et al.* [20]	15 months	Male	• Tips of little fingers of both hands • Right foot (second and third toes) • No coronary involvement	IVIG	Pentoxyphylline	Autoamputation	No comment
Soni *et al.* [2]	4 year	Male	• Dilated aortic root and left ventricular dysfunction • Gangrene of lower lip and left index finger	IVIG	LMWH Aspirin	Gangrene improved	Aortic root dilatation persisted on 6 month follow up
Al Tasseh *et al.* [3]	14 months	Male	• LCA dilatation (child also had factor V leiden mutation) • Dry gangrene of second and third finger right hand	IVIG Pulse steroid (3 days)	Aspirin PGE1 Enoxaparin	Autoamputation of gangrenous part	Echo normal on follow up
Mohsin *et al.* [21]	10 months	Male	• Dilated left main coronary artery (child had underlying VSD) • Gangrene of left big toe	IVIG one dose	Aspirin LMWH TNG	No comment	No comment
Garrido-García *et al.* [22]	<3 months	–	• Coronary artery • Gangrene of toes of right foot	(Study from Mexico mentioned one patient with KD and peripheral gangrene, details of treatment given to this particular patient and follow up not mentioned)			

(continued)

Table 1. (continued)

Study	Age	Sex	Gangrene/blood vessel involved	Anti-inflammatory therapy	Anti-thrombotic/ thrombolytic therapy	Outcome	Follow up status
Tahghighi *et al.* [23]	8 months	Female	• Coronary ectasia • Necrotic ulcer over left knee	IVIG (two doses) Methyl pred	Aspirin	Improved	Coronary ectasia resolved on follow up
Present case 1	14 months	Male	• Feet gangrene • Coronary artery changes	IVIG (two doses) Methyl pred	Aspirin LMWH	Amputation of gangrenous part	Coronary dilatation improved
Present case 2	6 months	Male	• Left hand gangrene	IVIG (two doses) Methyl pred Infliximab	Aspirin LMWH	Autoamputation	ECHO normal on follow up
Present case 3	2 months	Female	• Finger tips of left hand and toes of lower limb	IVIG Methyl pred	LMWH Aspirin	Discharged with minimal gangrene	Mild tricuspid regurgitation
Present case 4	2 months	Male	• Left lower limb gangrene • Right toe gangrene	IVIG Methyl pred	LMWH Aspirin	Improved, only residual gangrene	Normal on follow up

Notes: IVIG, intravenous immunoglobulin; tPA, tissue plasminogen activator; PGE1, prostaglandin 1; TNG, topical nitroglycerine; LCA, left coronary artery; RCA, right coronary artery; Methylpred, methylprednisolone; LMWH, low molecular weight heparin; VSD, ventricular septal defect; ECHO, echocardiography.

Biological agents can be used in cases non-responsive to first line therapy or in rapidly progressive gangrene to restrict tissue damage to minimum.

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