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RESEARCH

Concurrent infections in children with Kawasaki disease: lessons learned over 26 years

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Abstract

Etiology of Kawasaki disease (KD) remains an enigma despite more than 50 years of extensive research. There is evidence that concurrent infections may play a role in the pathogenesis of KD. The present study reports various infections identified in a large cohort of patients with KD in Northwest India. We reviewed case records of patients with KD from January 1994 to February 2020. Patients with KD identified to have concurrent infection at presentation were analyzed in detail. Of 878 cases of KD during this period, 88 (60 boys, 28 girls; 64 incomplete KD, 24 complete KD) had evidence of concurrent infection. Infective manifestations included superficial and deep-seated abscesses (27.45%), pneumonia (28.4%), gastrointestinal manifestations (29.5%), urinary tract infection (4.5%), and septic arthritis (2.3%). Infectious agents were confirmed in 67/88 patients (76.13%) — these included bacteria ($n=51$), viruses ($n=13$), fungi ($n=2$), and protozoa ($n=1$). Among bacteria, infections with *Staphylococcus* sp. and *Streptococcus* sp. were the commonest (19/88 and 14/88 patients, respectively). Eighty-one children were treated with intravenous immunoglobulin (IVIg, 2 g/kg) and aspirin. Coronary artery abnormalities (CAAs) were seen in 11/88 patients (12.5%) during the acute phase — these normalized at 6 weeks of follow-up in all patients. To conclude, concurrent infections were seen in 10% of patients with KD at our center. If the clinical presentation suggests KD, one should not exclude the diagnosis even if there is evidence of an accompanying infection. Although 12.5% of patients with infection-associated KD had CAAs, none had persistent CAAs at 6 weeks of follow-up.

Keywords Kawasaki disease · Concurrent infection · Bacterial infection · Viral infection · Coronary artery abnormalities · India

Introduction

Kawasaki disease (KD) is a common childhood vasculitis [1, 2]. It has been more than 55 years since the first description of KD in Japanese children by Dr. Tomisaku Kawasaki [3, 4]. However, the pathogenesis of KD is still an enigma.

Key messages

- Concurrent infections in the context of KD often lead to diagnostic dilemmas for the attending pediatrician and may result in delays in treatment.
- The increased incidence of CAAs in infection-associated KD may be because of these delays in the administration of intravenous immunoglobulin.
- This infection may be a possible trigger for KD. One should not exclude the diagnosis of KD even if there is an associated infection.

Several hypotheses have been proposed for the etiopathogenesis of KD [5]. It has been proposed that KD occurs due to an infectious or environmental trigger in a genetically predisposed individual [6–13]. Recent studies have documented a decline in KD cases during the COVID-19 pandemic compared to previous years [6]. This may be due to the decrease in common respiratory infections among young children during the pandemic as a result of physical distancing, universal masking, and being confined to home [6]. In an autopsy study, Rowley et al. reported the identification of inclusion bodies from the respiratory epithelium in a patient with KD who had died in road traffic accidents [14, 15]. Several other workers have also shown an association between respiratory viral infection and KD [16–19]. Seasonal peaks in the incidence of KD reported from some countries also point towards a possible infective etiology

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[20, 21]. However, a causal relationship with a specific infectious agent has not been proven so far [22].

Several bacterial and viral pathogens have been associated with the pathogenesis of KD. These include *Streptococcus* sp., *Staphylococcus* sp., *Klebsiella* sp., enterovirus, rhinovirus, adenovirus, Epstein-Barr virus (EBV), bocavirus, influenza virus, and coxsackievirus.[23] Herein, we report associated infections identified in our cohort of patients with KD over the last 26 years.

Methodology

A review of records of children with KD diagnosed at a tertiary care federally funded teaching institute from North West India was carried out. The period under review was January 1994 – February 2020. Diagnosis of complete and incomplete KD was based on American Heart Association (AHA) guidelines [1, 24, 25]. Of all cases of KD during this period, patients who had evidence of infection at presentation were subsequently analyzed for demography, clinical manifestations, laboratory features, treatment, complications, and long-term outcomes. 2D-transthoracic echocardiography (TTE) was performed during the acute phase and at follow-up. *Z*-scores for the coronary arteries were determined using body surface area-based measurements as outlined by Dallaire et al. [1]. Since 2013, we have also been carrying out computed tomography coronary angiography (CTCA) (using a 128-slice dual-source CT scanner with radiation optimization) in children with significant CAAs [26, 27].

Data were entered in a predefined Microsoft Excel sheet. Variables showing a normal distribution were expressed as means and standard deviations. Those not following normal distribution were expressed as the median and interquartile range (IQR). Parametric tests (ANOVA, *t*-test) were used to analyze normally distributed data. The association between two categorical variables was analyzed by chi-square tests. A p-value of < 0.05 was considered significant. Data were analyzed in SPSS software version 26.

Results

Of the 878 patients with KD during the study period (January 1994 – February 2020), 88 (10.02%) patients had evidence of concurrent infection. Median age of patients with infection-associated KD at diagnosis was 4.5 years (range 0.03–14.0 years). Male female ratio was 2.1:1. Median interval between the onset of fever and diagnosis of KD was 14 days (IQR, 5–15 days). Complete KD was diagnosed in 24 patients and incomplete KD in 64 patients. Among the 64 patients with incomplete KD, 54 had elevated CRP and/or ESR plus three or more laboratory findings, while 10 had elevated CRP or ESR along with positive TTE changes.

Principal clinical features

All patients had fever at presentation. Periungual desquamation was noted in 81/88 patients (92.04%). Oromucosal changes were noted in 53/88 (60.22%), maculopapular rash in 48/88 (54.54%), cervical lymphadenopathy in 42/88 (47.72%), conjunctival injection in 26/88 (29.54%), and dorsal edema of hands/feet in 13/88 patients (14.77%). Perianal desquamation was observed in 13/88 cases (14.77%%), and perianal rash was noted in 2/88 patients (2.27%). Cervical adenopathy was present in 42/88 (52.38%) patients. It was unilateral in 22/42 (52.4%), and bilateral in 20/42 (47.6%).

Among the 64 cases of incomplete KD, we observed periungual desquamation in 60 patients, oromucosal changes in 29, maculopapular rash in 28, cervical lymphadenopathy in 20, dorsal edema in 7, and sterile pyuria in 4 patients.

Other clinical manifestations

These included respiratory distress (25/88; 28.4%) and gastrointestinal manifestations (26/88; 29.54%). Irritability was noted in 21/88 patients (23.86%) — 5 of these were infants. Nine (10.22%) patients were diagnosed to have shock — *Staphylococcus aureus* was isolated in 4, while 1 patient each had *Pseudomonas aeruginosa* and *Acinetobacter baumanii*. Isolated hepatomegaly was noted in 11 patients (12.5%) and 7 (7.95%) had hepatosplenomegaly. Amongst the latter, Epstein Barr Virus (EBV) and Dengue infection were noted in 2 patients each, and 1 each had staphylococcal infection with macrophage activation syndrome (MAS), influenza with MAS, and KD shock syndrome. None of the patients with infection-associated KD developed BCG reactivation.

Other atypical features noted in our cohort included seizures ($n = 3$), cerebral infarct ($n = 1$), patchy demyelination in varicella-associated KD ($n = 1$), relapse of nephrotic syndrome ($n = 1$), autoimmune hepatitis ($n = 1$), digital gangrene ($n = 1$), and MAS ($n = 1$). Nine patients (10.22%) had arthritis — oligoarticular in 6, and monoarticular in 3. The most common joint affected was the knee [7], followed by ankle [4] and hip [2].

Microbiological profile

Microbiological evidence of concurrent infection was noted in 67/88 patients (76.13%) (Table 1). Bacterial infections were found in 51/67 patients (76.11%), whereas viral, fungal, and protozoal infections were noted in 13/67 (19.4%) respectively. Twenty-one patients had distinct foci

Table 1 Source of isolated organisms in children with Kawasaki disease and concurrent infection

Source	Number of patients ($n=67$) (%)
Throat swab culture	13 (19.4%)
Blood culture	10 (14.9%)
Pus culture	17 (25.3%)
Urine culture	4 (5.9%)
Tracheal fluid culture	2 (2.9%)
Blood serology	20 (29.8%)
CSF mycobacterium gene X-pert	1 (1.49%)

Abbreviations: *CSF*, cerebrospinal fluid

of infection at presentation — these included abscesses (superficial or deep), osteomyelitis, pneumonia with empyema, and suppurative lymphadenitis (Table 2). However, no organism could be isolated in these patients (Table 3).

Table 2 Distribution of various microorganisms in patients with Kawasaki disease and concurrent infections

Pattern of infection	Number of patients ($n=67$)
Bacterial infections (51)	
Staphylococcus aureus	17
Staphylococcus hominins	2
Alpha hemolytic streptococcus	5
Beta hemolytic streptococcus	9
Pseudomonas sp.	2
Acinetobacter sp.	2
Burkholderia sp.	2
Escherichia coli	4
Salmonella sp.	1
Enterococcus faecalis	2
Klebsiella sp.	2
Mycobacterium sp.	1
Mycoplasma sp.	2
Viral infections [13]	
Dengue	4
Hepatitis A	1
Epstein Barr virus	1
Measles	2
Varicella	1
Enterovirus	1
Influenza (H1N1)	2
Herpes simplex virus	1
Fungal infections [2]	
Candida sp.	2
Protozoal infections [1]	
Malaria	1

Table 3 Distribution of focus of infection in patients with Kawasaki disease where microorganism could not be isolated

Site of infection		Number of patients ($n=21$)
Abscess	Superficial	9
	Deep	5
Pneumonia with empyema		4
Osteomyelitis		1
Ear discharge		1
Septic arthritis		1

Complete blood counts showed median hemoglobin of 94 g/L (range 57– 142) and median total leucocyte counts of 14.9×10^9/L (range 2.1–45.6). Sixty-three patients (71.59%) had leukocytosis ($>11\times10^9$/L), while 2 (2.27%) had leucopenia ($<4\times10^9$/L). Neutrophilic predominance was noted in 65 patients. Thrombocytosis was reported in 60 (68.18%) patients with median platelet counts of 615×10^9/L (range 163–1397). C-Reactive protein (CRP) values were elevated in all patients. Elevated transaminases were seen in 44 (50%) patients. Hypoalbuminemia (serum albumin < 35 g/L) was noted in 51 (57.95%) with a median serum albumin 31 g/L (range 13–49). Hyponatremia was noted in 40/88 patients (45.4%). Sterile pyuria and distended gall bladder were seen in 6/88 (6.81%) and 14/88 patients (15.90%), respectively.

Cardiovascular complications

CAAs were noted in 11/88 patients (12.5%). The left main coronary artery (LMCA) was involved in 7, followed by the left anterior descending (LAD) ($n=4$) and right coronary artery (RCA) ($n=4$). While 1 patient had involvement of all the coronary arteries, involvement of both LMCA and LAD was found in 2 cases. All patients with CAAs, except 1, had small aneurysms (Z score ranging from + 3.39 to 4.5 Z). One patient had a medium-sized aneurysm in RCA (+ 5.5Z). Three patients had involvement of multiple coronary arteries— LMCA, LAD, and RCA in 1; LMCA and LAD in 1; LMCA and RCA in 1. Loss of tapering, perivascular brightness, and pericardial effusion were noted in 1 patient each. Two patients had low ejection fraction (22% and 28%, respectively) at presentation but this had normalized at 6 weeks of follow-up. CTCA was performed in 5 patients. One patient had a fusiform aneurysm in LAD on CTCA while the remaining 4 patients showed no additional findings (Fig. 1).

Treatment details

Eighty-one patients (92.04%) were treated with intravenous immunoglobulin (IVIg) (@2 g/kg over 12–18 h) along with low-dose aspirin (3–5 mg/kg/day). IVIg was administered

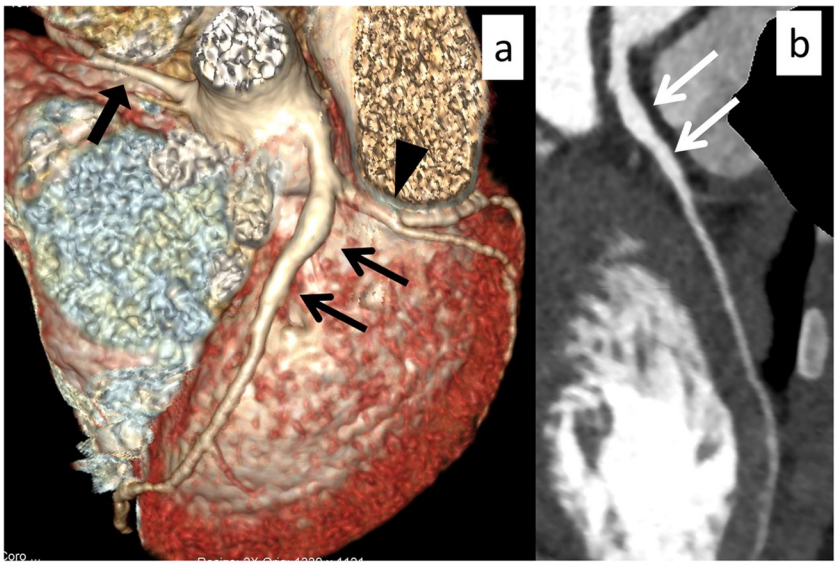

Fig. 1 CT coronary angiography (CTCA) volume rendered (VR) (**a**) and curved reformatted (CPR) (**b**) images in a 9-year-old boy with KD at presentation shows fusiform aneurysm in proximal left anterior descending coronary artery (arrows in **a** and **b**). Note the normal right coronary (thick arrow) and left circumflex coronary (arrow head) arteries

at a median 15th day of illness (range 7–38). Seven patients were not treated for KD due to spontaneous defervescence and normalization of inflammatory parameters at the time of their presentation to our hospital. Adjunctive therapy was required in 7 patients (7/81; 8.64%). This included infliximab ($n=2$), methylprednisolone pulse therapy ($n=2$), methylprednisolone pulse therapy along with infliximab ($n=1$), methylprednisolone pulse therapy along with 2nd dose of IVIg ($n=1$), and infliximab with 2nd dose of IVIg ($n=1$).

Outcome

The duration of follow-up of patients with infection-associated KD was 5280 patient months. None of the patients with infection-associated KD had residual CAAs on follow-up. There was no mortality in the cohort.

Discussion

In this study we have shown one-tenth of patients with KD at a tertiary care center in North India had evidence of concurrent infection. It is well-recognized that the presence of an infection does not rule out the diagnosis of KD [1, 2, 7, 9, 11, 12, 14–19]. However, most of the published literature on this aspect is in the form of clinical case reports. There is a paucity of large cohort studies on concurrent infections in children with KD. It is particularly important for pediatricians working in less developed regions of the world to be aware of this, as infections are rather common among young children in these countries.

We found that 76.11% patients with infection-associated KD in our cohort had bacterial infections. Viral infections were seen in 19.40%. Previous studies have shown a predominant association between KD and respiratory viral infections such as influenza virus, parainfluenza virus, metapneumovirus, adenovirus, and bocavirus [13, 28–32]. However, in our study, we found dengue virus, measles, herpes, EBV, varicella, enterovirus, and influenza to be more common. Comprehensive respiratory panel testing for viruses was not carried out for any of the patients in our cohort as this was unavailable. This may be the reason for the difference in the profile of viral infections in our cohort as compared to the previously published studies. Further, geographical differences in viral and bacterial profiles could also significantly influence the spectrum of infections associated with KD. Differences in viral and bacterial profiles between tropical and other countries could also contribute to the observed variations in the etiology of KD across different regions [33].

The commonest bacterial isolates in our study were *Staphylococcus* sp. and *Streptococcus* species. Previous studies have shown an association between staphylococcal infection and KD. It is believed that staphylococcal and streptococcal superantigens may have a role in triggering the cytokine cascade and this may manifest as KD [34–36].

It is believed that splenomegaly is unusual in patients with KD unless there is secondary macrophage activation syndrome (MAS) [37]. In fact, the diagnosis of KD is considered to be unlikely in the presence of splenomegaly [1, 38, 39]. However, 7 patients in our cohort had splenomegaly— 3 among these had MAS, 2 had dengue, and 2 had EBV infection. Therefore, even in the presence of splenomegaly, in some situations, the diagnosis of KD may still need to be considered [40]. Atypical findings in our cohort included gangrene ($n=1$), brain parenchymal demyelination ($n=1$) (varicella), seizures ($n=1$) (tubercular meningitis), relapse of nephrotic syndrome ($n=1$)

Table 4 Review of literature on concurrent infections in patients with Kawasaki disease

S. no	Author details/year/country	Age median (range) Mean ± SD	Day of diagnosis from onset of fever	Study population	Incomplete KD	Spectrum of infections	Coronary involvement	Treatment
	Bajolle F et al., 2014, France [41]	2 (0.5–9) years	Not available	Total KD patients, 32 KD with Bocavirus infection, 7 (21.8%) Adenovirus infection, 1 (3.1%)	Not available	- **3** had **Bocavirus** DNA in serum - 7 had **Bocavirus** DNA in nasopharyngeal secretion - **6** had elevated viral load of **Bocavirus** - **1** had **Adenovirus** isolated from nasopharyngeal secretion	12/32 (37.5%)	Not available
	Turnier JL et al., 2015, Colorado, USA [42]	2.92 (1.48–4.55) years	6 (5–8) days	Total KD patients. 222 KD with respiratory viral infection. 93 (41.9%)	29/93 (31.2%)	- Adenovirus, 9 (4.7%) - Coronavirus 229E, 2 (1%) - Coronavirus NL63, 3 (1.6%) - Coronavirus OC43, 2 (1%) - Human metapneumovirus, 9 (4.7%) - Influenza A, 6 (3.1%) - Influenza B, 3 (1.6%) - Parainfluenza 1, 2 (1%) - Parainfluenza 2, 6 (3.1%) - Parainfluenza 3, 2 (1%) - Parainfluenza 4, 7 (3.6%) - Respiratory Syncytial Virus, 9 (4.7%) - Rhinovirus/enterovirus, 54 (28.1%)	16/93 (17.2%)	All patients received IVIg IVIg resistant, **19 patients** (20.7%)
	Suenaga T et al., 2009, Japan [43]	24.6 months	Not available	Total KD patients, 60 KD with infection, 44 (73.3%)	NA	- ***Streptococcus pyogenes*** superantigens were detected in stool specimen, 42/44 - ***Staphylococcus aureus*** was detected in throat swab, 2/44	Not mentioned	Not mentioned

Table 4 (continued)

S. no	Author details/year/country	Age median (range) Mean ± SD	Day of diagnosis from onset of fever	Study population	Incomplete KD	Spectrum of infections	Coronary involvement	Treatment
	Lee MN et al., 2011, Seoul, South Korea [44]	5.5 ± 3.5 years	9.2 ± 4.7 days	Total KD patients, 358 KD with pneumonia, 54 (15%) KD with *Mycoplasma pneumoniae* infection, 12 (3.3%)	NA	- **Anti-mycoplasma** antibody titers were elevated in 12 patients out of 54 patients with pneumonia	Not mentioned	IVIg and aspirin
	Matsubara K et al., 2006, Japan [45]	23 ± 19.5	4.7 ± 2 days	Total KD patients, 65 Total serum samples (in clinical days 1–28), 293	NA	Significant elevation of IgM antibody levels against - **Staphylococcal enterotoxin A**; **staphylococcal enterotoxin B; staphylococcal enterotoxin C;** - **Toxic shock syndrome toxin-1 and** - **Streptococcal pyrogenic exotoxin A**	4/65 (6.15%)	All patients were treated with IVIg and aspirin **4 patients** were treated with 2nd dose of IVIg
	Chang LY et al., 2014, Taiwan [23]	2.07 ± 1.76 years	7.5 ± 2.4 days	Total KD patients, 228 KD with viral infections- 119 (52.7%) (**Both by viral isolation and PCR**)	NA	- Enterovirus, 40 (17.7%) - Adenovirus, 18 (8%) - Human rhinovirus, 60 (26.5%) - Human metapneumovirus, 5 (2.2%) - Coronavirus, 16 (7.1%) - Influenza A, 2 (0.9%) - Influenza B, 2 (0.9%) - Parainfluenza 3, 3 (1.3%)	28/228 (12%)	All patients received IVIg (2 g/kg) and low dose of aspirin (3–5 mg/kg/day) 2nd dose of IVIg, **14 patients (6.2%)**
	Jordan-Villegas A et al., 2010, Texas, USA [46]	3.4 (1.2–4.5) years	7 (5–8) days	Total KD patients, 394 Viral testing was performed in 251/394 patients (63.7%) KD with viral infections, 22/251 (8.8%)	8/22 (36%)	- Rhinovirus, 6/22 (27.3%) - Adenovirus, 6/22 (27.3%) - Influenza A/B, 5/22 (22.7%) - Parainfluenza 1–3- 3/22 (13.6%) - Respiratory Syncytial virus, 2/22 (9.1%)	12/22 (54.5%)	All patients received IVIg (2 g/kg) and aspirin 2nd dose of IVIg (IVIg resistance), **4 patients (18%)**

Table 4 (continued)

S. no	Author details/year/country	Age median (range) Mean ± SD	Day of diagnosis from onset of fever	Study population	Incomplete KD	Spectrum of infections	Coronary involvement	Treatment
8	Cohort from PGIMER, 2024, India	4.5 (0.03–14) years	14 (5–15) days	Total KD patients, 878 KD with infection, 88 (10.02%)	64/88 (72.73%)	- Most common bacterial infections, **staphylococcal** (19/88)/**streptococcal** (14/88) - Most common viral infections, **dengue** (4/88)	11/88 (12.5%)	81/88 patients (92%): single dose of IVIg 2/88 patients (2.27%): IVIg and infliximab 2/88 patients (2.27%): IVIg and methylprednisolone pulse 1/88 patients (1.13%): IVIg and methylprednisolone pulse and infliximab 1/88 patients (1.13%): 2 doses of IVIg and methylprednisolone pulse 1/88 patients (1.13%): 2 doses of IVIg and infliximab

Abbreviations: *KD* Kawasaki disease, *DNA* deoxy ribonucleic acid, *PCR* polymerase chain reaction, *IVIg* intravenous immunoglobulin

(staphylococcal gluteal abscess), acute renal failure ($n=1$) (staphylococcal subcutaneous abscess).

We observed that the median age of diagnosis, delays in diagnosis, and incomplete presentation of KD were much higher than the published literature (Table 4). In low-income and middle-income countries, children with a febrile illness are often pre-emptively treated with antimicrobials, as infections are widespread. As a result, children with KD may remain undiagnosed for several days [12–14].

We observed CAAs in 12.5% of patients. Most patients had a small-sized aneurysm, while only 1 had a medium-sized aneurysm. However, normalization of coronaries was noted in all patients over the next 6 weeks of follow-up. The prevalence of CAAs in infection-associated KD cohorts varies widely across published studies (Table 4). Reported prevalence range from as low as 6.15% to as high as 54.5% (Table 4). A recently published prospective study by Mahajan et al. showed the incidence of CAAs in 40% of patients with infection-associated KD in their cohort. [33] Furthermore, 20% of the patients in their cohort continued to have CAAs, although the sample size was very small ($n=10$) in this study [33]. Chang et al. found that patients with KD in the context of viral infections had a more severe disease course and a greater likelihood of cardiac involvement. [23] Turnier et al., however, found no significant difference in disease severity, cardiac manifestations, and IVIg resistance between KD patients with and without viral infection [42]. Concurrent infections in the context of KD often lead to diagnostic dilemmas for the attending pediatrician and may result in delays in treatment. The increased incidence of CAAs in infection-associated KD may be caused by delays in the administration of IVIg. [31–34, 47]

Although some of the clinical findings of KD (e.g., fever, cervical adenopathy, rash) can indeed be seen in isolation in several infectious illnesses, the typical constellation of clinical findings and the characteristic temporal sequence of appearance of clinical features observed in KD do not occur in any infectious illness [2, 7–9, 11–13]. For experienced clinicians and centers with adequate expertise in managing the condition, diagnosing KD is usually not difficult. Our center has been involved in the management of KD for the past 30 years, and we follow the largest cohort of KD in India.

This is the first major study on KD with concurrent infections from the developing world. Previous studies on the subject have emerged from economically developed countries and have mostly focused on patients with KD and viral infections. However, our cohort showed a wide range of organisms associated with KD. The limitation of this study is that it is based on single-center retrospective data and the absence of comprehensive respiratory panel testing for viruses in this cohort.

Conclusions

Approximately one-tenth of all children with KD at our center had a concurrent infection, which may be a possible trigger for KD. One should not exclude the diagnosis of KD even if there is an associated infection. Timely initiation of specific therapy may lead to a favorable outcome of KD in these settings.

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Author contribution RKP: Conceptualization, writing of the initial draft, critical revision of the manuscript and final approval, patient management

SB: Writing of the initial draft, revision of the manuscript, and patient management.

AS, SM, AKJ, AT, GCv, PV, SV, SN, DS: Writing, editing of the manuscript, revision of the manuscript, and patient management.

MD, SaS, MS, AA, AR: Laboratory investigations, radiological investigations, writing and editing of the manuscript.

SS: Conceptualization, critical revision of the manuscript, patient management.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethical approval All procedures performed in studies involving human participants complied with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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

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