

Pulmonary presentation of Kawasaki disease—A diagnostic challenge

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Abstract

Objectives: Kawasaki disease (KD) is a multisystemic vasculitis with predominant mucocutaneous manifestations. Pulmonary involvement in KD is distinctly uncommon and is not commonly recognized. We describe our experience of managing children with KD wherein the initial presentation was predominantly pulmonary.

Methods: Six hundred and two children have been diagnosed with KD during the period January 1993 to May 2017 in the Allergy Immunology Unit, Advanced Pediatrics Centre, Postgraduate Institute of Medical Education and Research, Chandigarh. Data were collected from inpatient records in Allergy Immunology Unit and follow-up files in the Pediatric Rheumatology Clinic.

Results: Of 602 children, 11 (1.83%) had a predominant pulmonary presentation of KD. Mean age at diagnosis of KD was 2.5 years. Fever, cough and respiratory distress were the presenting complaints in all patients. First sign of KD was noted at a mean duration of 14.5 days from the onset of symptoms. Periungual desquamation was the most common clinical sign (72.7%). Persistent fever in spite of antimicrobials, thrombocytosis, and elevated erythrocyte sedimentation rate and C-reactive protein levels pointed toward a diagnosis of KD in our patients. Parenchymal consolidation was evident on chest X-ray in all patients, pleural effusion in six, empyema in three, and pneumothorax in two patients. Coronary artery abnormalities were evident in three patients. Intravenous immunoglobulin was given after a mean period of 22.4 days of onset of fever.

Conclusions: The diagnosis of KD is often delayed in children who have a predominantly pulmonary presentation. This can have adverse clinical consequences.

KEYWORDS

coronary artery abnormalities, intravenous immunoglobulin, Kawasaki disease, pneumonia

1 | INTRODUCTION

Kawasaki disease (KD) is a medium vessel multisystemic vasculitis that predominantly affects children below 5 years. The diagnosis of KD is based on the following criteria: presence of fever for ≥ 5 days and four

or more of the five principal clinical features which include polymorphous exanthem, extremity changes, mucosal changes involving the lips and oral cavity, bilateral bulbar conjunctival injection, and unilateral cervical lymphadenopathy, which appear sequentially in a cascade.¹ The diagnosis has to be made on clinical grounds alone as

there is no pathognomonic laboratory test for confirmation. The clinical course of KD can be divided into three phases²: (a) Acute febrile phase—lasts for initial 10–14 days; characterized by fever, mucocutaneous changes and other less commonly recognized findings such as hydrops of gall bladder, sterile pyuria and myocarditis; (b) Sub-acute phase—lasts from weeks 2–4 after symptom onset; characterized by periungual desquamation and coronary abnormalities along with resolution of principal clinical features; (c) Convalescent phase—characterized by complete resolution of clinical signs and laboratory parameters. Exact etiology of KD remains unknown, though various hypotheses on the role of micro-organisms and superantigens have been postulated.²

The principal features that constitute the diagnostic criteria are predominantly mucocutaneous. However, as KD is a vasculitis, it can involve several other organ systems including musculoskeletal, gastrointestinal, central nervous system, genitourinary, and pulmonary.^{2,3}

A proportion of children with KD may occasionally present with unusual clinical features (atypical KD), or may have fever in the presence of less than four principal clinical features (incomplete KD).⁴ The initial presentation may, at times, point toward a different disease but the child may develop KD during the course of illness. Pulmonary involvement in patients with KD is distinctly uncommon and is often not commonly recognized. Careful monitoring is essential because some features of KD may evolve over time and early recognition of this group of patients may prevent delays in diagnosis and allow institution of early appropriate therapy.

We describe our experience of managing children with KD wherein the initial presentation was predominantly pulmonary thereby resulting in considerable diagnostic difficulties and consequential delay in institution of appropriate therapy.

2 | PATIENTS AND METHODS

Six hundred and two (602) children were diagnosed with KD during the period January 1993–May 2017 in the Allergy Immunology Unit, Advanced Pediatrics Centre, Postgraduate Institute of Medical Education and Research, Chandigarh. Our institute is a not-for-profit federally funded teaching hospital and predominantly caters to patients from North West India.

The diagnosis of KD was based on the American Heart Association 2004 criteria. Data were collected from inpatient records in Allergy Immunology Unit and follow-up files in the Pediatric Rheumatology Clinic. Children with a predominant pulmonary presentation of KD were studied in detail. Pulmonary involvement was defined as presence of findings suggestive of pulmonary parenchymal (pneumonia) or pleural (pleural effusion, empyema, pneumothorax) involvement, either on clinical examination or on radiology, at presentation.

Clinical findings, laboratory parameters and radiological data were recorded. Laboratory investigations included total leukocyte count (TLC), platelet count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and serum aminotransferases. Radiological examination

included X-ray chest, ultrasonography (USG), computerized tomography (CT) of chest, wherever considered necessary and echocardiography to assess coronary arteries. All children were treated with intravenous antimicrobials for pneumonia and/or pleural effusion/empyema. Following a diagnosis of KD, intravenous immunoglobulin (IVIG) was administered at 2 g/kg along with aspirin at 30–50 mg/kg/day which was continued until ≥ 48 –72 h after fever cessation. The aspirin dose was thereafter reduced to 3–5 mg/kg/day and continued for the next 6–8 weeks. Aspirin was discontinued if the follow-up echocardiography did not show any coronary artery abnormality.

3 | RESULTS

Of 602 children, 11 (1.83%) had a predominant pulmonary presentation of KD. Mean age at diagnosis of KD was 2.5 years (range 6 months–4 years). Clinical findings are summarized in Table 1. There were six girls and five boys. Fever, cough, and respiratory distress were the presenting complaints in all patients with mean duration of symptoms at presentation being 14.1 days (range 3–45 days). Clinical history compatible with diagnosis of KD was available in only four patients—one had redness of tongue and oral mucosa (Patient 4), one had redness of lips and tongue along with edema over dorsum of feet (Patient 5), one had rash and irritability (Patient 10), while one patient had redness of eyes (Patient 11). Of these, only two patients had signs (rash and desquamation) to suggest a diagnosis of KD at presentation (Patients 4 and 10). Rest (63.6%) of the patients had no features suggesting a diagnosis of KD either on history or at presentation.

First sign of KD was noted at a mean duration of 14.5 days (range 1–28 days) from the onset of symptoms. Periungual desquamation was the most common clinical sign seen in eight patients (72.7%) that suggested a diagnosis of KD, followed by erythematous rash in four patients and perianal desquamation in three patients each, while one patient had extensive desquamation involving bilateral plantar surfaces. Persistent fever in spite of antimicrobials, thrombocytosis, and elevated ESR and CRP levels were other features that pointed toward a diagnosis of KD in our patients. One patient had no discernible signs of KD at presentation. However, he continued to have persisting fever in spite of antimicrobials, a raised CRP and subsequently developed thrombocytosis. A diagnosis of KD was proffered at this stage and he was given IVIG after which there was prompt resolution of symptoms.

Mean maximum TLC was 25 009 cells/mm³ (Table 2). Thrombocytosis was evident in all patients—mean maximum platelet count was 886 545/ μ L. Acute phase reactants were elevated (mean ESR and CRP was 53.75 [$n = 8$] and 140.5 [$n = 10$], respectively), thereby indicating a state of hyper-inflammation in the cohort. Transaminitis was seen in two patients while sterile pyuria was present in one patient. Only two patients had evidence of infection on microbiological work up—one patient grew methicillin sensitive *Staphylococcus aureus* in pus while other had a positive *Mycoplasma agglutinin* titre.

All patients were analyzed radiologically with X-ray chest and USG. Pneumonia was the initial diagnosis in all patients. Parenchymal

TABLE 1 Clinical findings in patients with pulmonary presentation of KD

	1	2	3	4	5	6	7	8	9	10	11
Age (in years)/gender	4/F	2/F	1/M	3/F	4/M	0.75/M	4/F	3.5/F	4/F	0.5/M	1/M
Presenting complaints											
(a) Fever	+	+	+	+	+	+	+	+	+	+	+
(b) Cough	+	+	+	+	+	+	+	+	+	+	+
(c) Tachypnea	+	+	+	+	+	+	+	+	+	+	+
Duration of symptoms (in days)	10	13	3	45	21	18	10	6	20	4	5
Symptoms suggestive of KD prior to presentation	-	-	-	Redness of tongue and oral mucosa	Red lips and tongue	-	-	-	-	Rash, irritability	Redness of eyes
Symptoms suggestive of KD at time of presentation	-	-	-	Rash, desquamation	-	-	-	-	-	Rash, irritability	-
Interval between symptom onset and onset of 1st symptom/sign of KD (in days)	28	15	6	6	15	0	18	20	24	3	1
Interval between presentation and diagnosis of KD (in days)	18	2	15	1	3	8	8	14	4	10	6
Examination findings suggestive of KD											
(a) Rash	-	+	+	+	-	-	-	-	-	+	-
(b) Reddened lips	-	-	-	-	-	-	+	-	-	-	-
(c) Perianal desquamation	-	+	+	-	-	-	+	-	-	-	-
(d) Periungual desquamation	+	+	-	+	+	-	-	+	+	+	+

M, male; F, female.

consolidation was evident on chest X-ray in all patients. This radiological picture was no different from that seen in other common forms of childhood pneumonia (eg, staphylococcal or pneumococcal pneumonia). All except two (81.8%) had complications evident on USG or X-ray chest in the form of pleural effusion in 6 (54.5%), empyema in 3 (27.3%), and pneumothorax in 2 (18.2%) (Table 2). Four patients

underwent computerized tomography of chest and the findings were largely compatible with those seen on X-ray chest.

Coronary artery abnormalities were evident on echocardiography in three patients. Dilatation of right coronary artery, ectasia of left main coronary artery, and bright coronaries were noted in one patient each. Repeat echocardiography after 2 and 6 weeks was normal in two

TABLE 2 Laboratory findings in patients with pulmonary presentation of KD

	1	2	3	4	5	6	7	8	9	10	11
Maximum platelet count ($\times 10^9/L$)	7.27	12.7	9.0	6.39	14.93	9.2	7.46	14.48	7.1	2.93	6.06
Maximum ESR (mm 1st hour)	-	49	67	45	29	53	72	28	87	-	-
Maximum CRP (mg/L)	144	153	274	59	26	65	234	94	82	273	-
Chest X-ray findings											
(a) Consolidation		+	+	+	+	+	+	+	+	+	+
(b) Pleural effusion		-	+	+	+	+	-	-	-	+	-
(c) Empyema		+	-	-	-	-	-	+	+	-	-
(d) Pneumothorax		-	+	-	-	-	-	-	+	-	-

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

TABLE 3 Treatment proffered to patients with pulmonary presentation of KD

	1	2	3	4	5	6	7	8	9	10	11
Intravenous antimicrobials	+	+	+	+	+	+	+	+	+	+	+
ICDT	+	+	-	+	-	-	-	+	+	-	-
Intraleural Streptokinase	+	-	-	-	-	-	-	+	+	-	-
Surgical intervention	+ VATS	-	-	-	-	-	-	-	+ decortication	-	-
Aspirin	+	+	+	+	+	+	+	+	+	+	+
Day of administration of IVIG after symptom onset	30	17	12	50	26	16	19	21	25	18	13
Need for 2nd dose of IVIG	-	-	+	-	-	-	+	-	-	-	-

ICDT, inter-costal drainage tube; VATS, video-assisted thoracoscopic surgery; IVIG, intravenous immunoglobulin.

patients while one patient was lost to follow-up and repeat echocardiography could not be performed. Total follow-up period was 18 patient years.

Intravenous immunoglobulin (IVIG) at 2 g/kg was given after a mean period of 22.4 days of onset of fever (Table 3). Fever that had been unresponsive to intravenous antimicrobials, responded to IVIG therapy in all except two patients. The latter required a second dose of IVIG. All patients received aspirin at 30-50 mg/kg/day during the acute stage followed by low dose aspirin (3-5 mg/kg/day) for 4-6 weeks. Intravenous antimicrobials were administered to all patients for pneumonia. Additional management for pneumonia and/or its complications included inter-costal drainage tube (ICDT) insertion in five patients and streptokinase in 2. Surgical management was required in two patients with one each undergoing video-assisted thoracoscopic surgery (VATS) and decortication.

4 | DISCUSSION

Kawasaki disease being a multisystemic vasculitis, can have involvement of various organ systems. Children with KD presenting predominantly with gastrointestinal and pulmonary manifestations often have significant delays in diagnosis. This is because in the absence of typical signs and symptoms, KD is not considered in the differential diagnosis. Also, pulmonary presentation of KD is often

incomplete and atypical and results in diagnostic difficulties for the attending physician.

We have described 11 cases with KD who had presented with pulmonary manifestations. None of our patients had the typical cascade of clinical findings characteristic of KD. A diagnosis of KD was thought of when the fever persisted in spite of antimicrobials and the inflammatory parameters were found to be significantly elevated. Desquamation in KD usually appears first in perineal area during acute febrile phase followed by periungual desquamation during the subacute phase (weeks 2-4 after onset of symptoms).² Ten of our patients developed desquamation and provided a clue toward diagnosis. Laboratory investigations often provide useful clues toward the diagnosis of KD. The acute phase reactants (ESR, CRP, and platelet count) were elevated in all of our patients.

Pulmonary manifestations that have been described in patients with KD include bronchopneumonia,⁵ hydropneumothorax,⁶ and pleural effusion.⁷ Cases of pulmonary presentation of KD described in the literature have been summarized in Table 4. Lee et al reported chest X-ray abnormalities in 51.2% of patients with KD.⁸ Abnormal chest X-ray findings were seen in all of our patients. Pleural effusion was seen in 54.5% patients followed by empyema in 27.3% and pneumothorax in 18.2%. Lung involvement in KD may occur due to inflammation of vessels resulting in increased vascular permeability. However, the entire spectrum of radiological pulmonary manifestations seen in children with KD cannot be solely explained by vessel inflammation.

TABLE 4 Cases of pulmonary presentation of KD described in the literature

	Sengler et al (Germany, 2004)	Lee et al (Korea, 2011)	Leahy et al (Ireland, 2012)	Vaidya et al (India, 2015)	Present study
Number of patients	2	54	1	1	11
Mean age (years)	0.67	-	3	3	2.5
Mean interval between presentation and diagnosis of KD (in days)	24	-	10	32	8.1
Concomitant infection	0	12	1	0	2
CAAs on echocardiography	1	-	1	1	3
Day of administration of IVIG after symptom onset	-	-	14	33	22.4
Number of patients requiring 2nd dose of IVIG	0	0	0	0	2

CAAs, coronary artery abnormalities; IVIG, intravenous immunoglobulin.

The pathogenesis of KD has been linked to infection with *Streptococcus*,⁹ *Staphylococcus*,⁹ Epstein Barr virus,¹⁰ Coronavirus,¹¹ and Parvovirus¹² among several other micro-organisms. Bacterial superantigens have also been associated with the development of KD.¹³ However, no definite causal relationship has been established till date. Two of our patients showed evidence of infection with isolation of methicillin sensitive *S aureus* (MSSA) and mycoplasma. Mycoplasma infection has been reported in children with KD presenting with predominant pulmonary manifestations.⁸ Whether this micro-organism acts as a trigger or has a definite causal relationship remains to be seen.

Coronary artery abnormalities (CAAs) may be seen in 15-25% of untreated patients and account for long-term morbidities associated with KD.¹⁴ It can be brought down to less than 3% if diagnosed early and treated appropriately.¹ Coronary involvement is usually more common in infants and in those with incomplete or atypical presentation. Three patients (27.3%) in present series had CAAs despite institution of IVIG. It is possible that the coronary complications that occurred in our patients were due to delays in administration of IVIG because of atypical presentation of KD but this would remain conjectural.

Intravenous immunoglobulin is the mainstay of treatment for KD and should preferably be given within 10 days of the onset of illness.^{1,15} "Incomplete" or "atypical" presentation of KD results not only in delayed diagnosis but also delays in initiation of appropriate therapy. Pulmonary symptoms are usually initially treated with antimicrobials and highlight the importance of considering a diagnosis of KD in children where fever persists for 4 or more days despite antimicrobials. The presence of relatively uncommon clinical features should not be a deterrent in considering underlying KD in such patients.

The strengths of this study are that this was a single centre study and all patients were diagnosed by the same set of clinicians (SS, DS) using standard guidelines. Management protocols were also uniform. The limitation of this study is the small sample size—this is inevitable considering the fact that data were collated from only one center and pulmonary manifestations of KD are a distinctly unusual presentation of this disorder.

5 | CONCLUSIONS

Various organ systems can be involved in KD and uncommon pulmonary manifestations can sometimes be seen in children. Unresolving pneumonia in a child who continues to be febrile despite adequate antimicrobials can be a clue toward the diagnosis of KD. In view of late recognition of symptoms, IVIG in such patients is often delayed resulting in significant morbidities. Physicians managing children with "difficult-to-treat" pneumonia should be aware of the unusual pulmonary presentation of KD as early recognition can prevent delays in diagnosis and shorten the hospital stay.

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