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CASE BASED REVIEW

Describing Kawasaki shock syndrome: results from a retrospective study and literature review

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Abstract Kawasaki shock syndrome (KSS) is a rare manifestation of Kawasaki disease (KD) characterized by systolic hypotension or clinical signs of poor perfusion. The objectives of the study are to describe the main clinical presentation, echocardiographic, and laboratory findings, as well as the treatment options and clinical outcomes of KSS patients when compared with KD patients. This is a retrospective study. All children referred to two pediatric rheumatology units from January 1, 2012, to December 31, 2014, were enrolled. Patients were divided into patients with or without KSS. We compared the two groups according to the following variables: sex, age, type of KD (classic, with less frequent manifestations, or incomplete), clinical manifestations, cardiac involvement, laboratory findings, therapy administered, response to treatment, and outcome. Eighty-four patients with KD were enrolled. Of these, five (6 %) met the criteria for KSS. Patients with KSS had higher values of C-reactive protein ($p = 0.005$), lower hemoglobin levels ($p = 0.003$); more frequent hyponatremia ($p = 0.004$), hypoalbuminemia ($p = 0.004$), and coagulopathy ($p = 0.003$); and increase in cardiac troponins ($p = 0.000$). Among the KSS patients, three had a coronary artery involvement, but none developed a permanent aneurysm. Intravenous immunoglobulin resistance was more frequent in the KSS group, although not significantly so (3/5, 60 % vs. 23/79, 30 %, P = NS). None of the five cases was fatal, and all recovered without sequelae. KSS patients are more likely to have higher rates of cardiac involvement. However, most cardiovascular abnormalities resolved promptly with therapy.

Keywords Coronary artery involvement · Heart failure · Hypotension · Kawasaki disease · Kawasaki shock syndrome

Introduction

Kawasaki shock syndrome (KSS) has been defined by Kanegaye et al. [1] as a rare Kawasaki disease (KD) manifestation characterized by systolic hypotension or clinical signs of poor perfusion due to cardiogenic and/or distributive shock [2, 3], slow capillary filling, myocardial dysfunction, and/or relative volume overload that requires fluid support and sometimes vasoactive drugs.

The etiology is unknown, probably multifactorial, but possible explanations suggest that KSS may be due to more intense vasculitis with capillary leak and the increased release of cytokines with myocardial dysfunction or systemic capillary leak syndrome [1, 4–9].

KSS seems to be under-recognized, but its prevalence may occur even in up to 5 % of patients with Kawasaki disease [1, 4, 10]. Studies have described the common characteristics of patients with KSS compared with patients with KD without KSS: patients with KSS are more likely to be females and to have earlier onset, incomplete presentations, and more severe laboratory abnormalities, particularly lower platelet counts, higher serum CRP levels, hyponatremia, increased transaminases, metabolic acidosis, consumptive coagulopathy, and lower serum albumin levels. These patients seem to have more often intravenous immunoglobulin (IVIG) resistance,

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requiring a second dose of IVIG or other additional treatments (corticosteroids or infliximab), and to have a higher risk of coronary artery involvement, mitral regurgitation, and prolonged myocardial dysfunction.

Herein, we describe a population of KD patients. The objectives of the study were to describe the proportion of KSS, the clinical presentations, the echocardiographic and laboratory findings, and the treatments and clinical outcomes of KSS compared to KD patients.

Material and methods

This is a retrospective study. All KD patients admitted to the Institute for Maternal and Child Health—IRCCS "Burlo Garofolo" of Trieste and to the Anna Meyer Children Hospital of Firenze, Italy, from January 1, 2012, to December 31, 2014, were enrolled. Enrolment criteria were the fulfilling of the mandatory presence of five or more days of fever plus at least four out of five diagnostic criteria for KD (rash, bilateral conjunctival injection, cervical lymphadenopathy, changes in oral mucosa and in the extremities) or at least three criteria plus coronary artery abnormalities documented through echocardiography as per the American Heart Association guidelines [11]. We excluded from the study all patients with positive bacterial cultures in normally sterile sites or with demonstrated viral or bacterial infections.

The patients with KD were then divided into two groups: the KD patients with shock (KSS group) and the patients without shock (KD group).

KSS was defined as the presence of hypotension and shock according to previously published guidelines. Following Kanegaye et al. [1], we diagnosed KSS if at least one of the following criteria was fulfilled: systolic hypotension for age (infants 0–28 days of age, <60 mmHg; infants 1–12 months of age, <70 mmHg; children 1–10 years of age, <70 mmHg + 2 × age; children >10 years of age, ≤90 mmHg) [12, 13], a decrease in systolic blood pressure from a baseline of ≥20 %, or clinical signs of poor perfusion (tachycardia, prolonged capillary refill, cool extremities, diminished pulses, oliguria, or mental status changes) regardless of measured blood pressure [14].

The data on all patients were collected from medical records.

For all patients, we gathered the following data: age, sex, days of fever at presentation and total days of fever, presence of complete or incomplete KD, recurrence of the disease, and the presence of the following less frequent findings: hydrops of the gallbladder, sterile pyuria, arthritis, pneumonia, abdominal involvement, or aseptic meningitis. The following echocardiographic data were also collected: cardiac or coronary involvement, coronary wall thickening, ectasia or aneurysm, ejection fraction reduction, mitral regurgitation, partial or diffused cardiac enlargement, and pericardial effusion. Among laboratory findings, the following parameters were evaluated: erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white blood cell, platelet count, hemoglobin levels, electrolytes, transaminases, γ-glutamyl transpeptidase, evaluation of coagulation function, markers of myocardial damage such as troponin, and albumin. Treatment and response to drug therapy were also analyzed: dose, timing of treatment, days of fever at first administration of IVIG, corticosteroid usage, and use of positive inotropic and vasoactive drugs.

Transthoracic echocardiography was performed with standard techniques during the acute (echocardiogram 1, 1–10 days after disease onset), subacute (echocardiogram 2, 11–21 days), and convalescent (echocardiogram 3, 22–90 days) phases and, later on, also in patients that developed coronary abnormalities (echocardiogram 4, 91–365 days).

Coronary arteries were classified as normal (luminal internal diameters of the right coronary and left anterior descending coronary artery measurement with echocardiography <2.5 SD from the mean normalized for body surface area; *Z* score <2.5), dilated (2.5 ≤ Z score < 4.0), or aneurysmal (dilatation of a coronary artery segment with a Z score of ≥4.0) [15].

We defined the lower limit of the reference range for the ejection fraction as 54 %.

We defined IVIG resistance as persistent or recrudescent fever ≥36 h after completion of the IVIG infusion (2 g/kg) [11].

All data have been saved in an Excel database. Statistical analysis was carried out with Stata/IC 12.1 (StataCorp LP, College Station, USA). To compare the characteristics of the two groups of patients, we adopted a Mann-Whitney rank-sum test for continuous variables and Fisher's exact test for dichotomous or categorical variables.

Results

Eighty-four patients were enrolled. The male/female ratio was 1.7:1. Median age at diagnosis was 27 months (interquartile range (IQR), 17–47) and median time of diagnosis from onset of fever was 6 days (IQR, 5–8). Five out of 84 patients presented KSS (6 %).

The two groups did not differ significantly in terms of demographic characteristics. There was no significant difference in classical clinical features at the time of presentation (rash, conjunctivitis, lymphadenopathy, changes in extremities and in oral mucosa).

However, all 5 patients with KSS showed at least one less frequent clinical sign, compared to 11 patients (14 %) in the KD group. Among the KSS patients, 3/5 patients presented abdominal pain with hydrops of the gallbladder in two cases and epathocholangitis in one case, 2/5 patients presented arthritis, 2/5 presented interstitial pneumonia, and 1/5 presented sterile pyuria. Although less frequent clinical presentations were more common in the KSS patients, only major abdominal involvement

was significantly more frequent in KSS ($p = 0.011$), occurring in 3/5 KSS patients (60 %) vs. 7/79 KD controls (9 %).

Echocardiographic abnormalities, mostly obtained during the acute phase, were more common in subjects with KSS. In particular, statistical significance was achieved for lower ejection fraction, areas of cardiac dyskinesia, areas of ischemia or infarction, and coronary artery abnormalities.

Demographic, clinical, echocardiographic, and outcome data are summarized in Table 1.

In both groups, the majority of the patients of both groups received IVIG at the dose of 2 g/kg within 10 days from onset. Although the comparison did not show statistically significant differences, the KSS patients presented more frequently IVIG resistance, requiring a second dose of IVIG or steroids. No patient in either group received treatment with TNF-alpha inhibitors or with anti-IL1.

In addition to KD standard therapy, as expected, all KSS patients received volume resuscitation (median 50 mL/kg) and 2/5 (vs. 0/79, $p = 0.003$) also received infusions of vasoactive agents such as milrinone, dobutamine, dopamine, and norepinephrine. Two KSS cases needed ventilatory support and 3 cases out of 5 were transferred to intensive care unit (ICU) vs. none of the 79 KD patients. The length of the ICU stay was 5, 7, and 12 days.

Patients with KSS remained hospitalized significantly longer with a median length of stay 4 days longer compared with KD subjects. None of the KSS patients was fatal. Regarding long-term outcomes, all abnormal cardiac parameters and echocardiographic findings found in the acute phase of the disease resolved in the subacute or convalescent phase and none of the children with KSS had persistent ectasia or aneurysms.

Table 1 Demographic, clinical, laboratory and ecochardiographic characteristics of patients with KSS and KD

Characteristic	KSS ($n = 5$)	KD ($n = 79$)	p
Age, median (IQR), months	25 (5–139)	27 (18–44)	0.932
Males, *n* (%)	4 (80 %)	49 (62 %)	0.647
Time at diagnosis, median (IQR), days of fever	6 (5–6)	6 (5–8)	0.871
Less frequent clinical features of KD, *n* (%)	5 (100 %)	11 (14 %)	0.000
Erythrocyte sedimentation rate, mm/h, median (IQR)	56.0 (34.5–67.5)	78.0 (53.5–101.0)	0.085
C-reactive protein, mg/dL median (IQR)	27.8 (23.3–96.0)	9.1 (5.5–16.2)	0.005
Hemoglobin level, g/dL, median (IQR)	8.1 (7.1–9.5)	11.0 (10.2–11.9)	0.003
Platelet count $\times 10^9$ cells per liter, median (IQR)	173 (83–500)	414 (356–524)	0.177
Hyponatremia, *n* (%)	4 (80 %)	12 (15 %)	0.004
Hypoalbuminemia, *n* (%)	3 (60 %)	8 (10 %)	0.015
Elevated cardiac troponin, *n* (%)	4 (80 %)	4 (5 %)	0.000
Elevated CPK-MB, *n* (%)	4 (80 %)	9 (11 %)	0.002
Consumptive coagulopathy	2 (40 %)	0	0.003
Coronary artery abnormalities, *n* (%)	3 (60 %)	13 (16 %)	0.045
Thickening of wall, *n* (%)	2 (40 %)	1 (1 %)	0.008
Ectasia, *n* (%)	1 (20 %)	10 (13 %)	0.513
Aneurysm, *n* (%)	0 (0 %)	2 (3 %)	1.000
Cardiac dilatation	1 (20 %)	2 (3 %)	0.170
Ejection fraction <54 %, *n* (%)	3 (60 %)	3 (4 %)	0.002
Mitral regurgitation, *n* (%)	1 (20 %)	11 (14 %)	0.547
Pericardial effusion, *n* (%)	2 (40 %)	10 (13 %)	0.147
Areas dyskinesia, *n* (%)	2 (40 %)	3 (4 %)	0.027
Areas ischemia or infarction, *n* (%)	2 (40 %)	2 (3 %)	0.016
Time from disease onset to IVIG <10 days, *n* (%)	4 (80 %)	68 (86 %)	0.547
Second dose of IVIG, *n* (%)	3 (60 %)	23 (29 %)	0.169
Steroids, *n* (%)	3 (60 %)	23 (29 %)	0.169
Vasoactive agents	2 (40 %)	0	0.003
Ventilatory support	2 (40 %)	0	0.003
Intensive care unit	3 (60 %)	0	0.000
Length of stay, median (IQR)	10 (8–14)	6 (4–8)	0.030
Death, *n* (%)	0	0	1.000

IQR interquartile range, *KD* Kawasaki disease, *KSS* Kawasaki shock syndrome

Discussion

KSS has recently received increased attention among pediatricians and pediatric rheumatologists. Although KSS is considered a rare clinical presentation of KD, the severity of cardiac involvement and the prominent vascular inflammation may lead to a higher incidence of coronary involvement compared with classic KD patients. However, this was not the case in our series.

Moreover, these patients are frequently misdiagnosed because of failure to recognize disease features, and clinical presentation may be mistaken for septic shock, with consequent delay in treatment [4].

For these reasons, it is important to increase the knowledge on KSS early diagnosis and treatment.

In our series, the prevalence of KSS was 6 % of patients with KD, which is quite similar to what was reported in previous studies [1, 4].

We compared KSS and classic KD patients. Although median age did not differ between the two groups, the majority of patients with KSS were younger than 6 months or older than 10 years (two patients were 5 and 3 months old, and two patients were 15 and 11 years old). It is important to underline that other studies did not show these findings [1, 4, 10], and on the contrary, patients with KSS presented a median age older than those without shock. Of note, previous studies have shown that children younger than 6 months and older than 9 years may manifest with minimal evidence of mucocutaneous inflammation and may present a higher rate of coronary artery disease, with higher prevalence of less frequent manifestations [16, 17]. Moreover, we would like to underline that less frequent (noncanonical) criteria were more common in KSS than in classic KD patients. This is of particular importance regarding the prognosis and the outcome of the disease; in fact, a prompt diagnosis is crucial in order to start the correct treatment and to prevent CAA. For this reason, pediatricians should be aware to recognize these less frequent criteria, especially in patients <6 months of age. It is also important to know that some rare criteria, such sterile pyuria, gallbladder hydrops, uveitis, hyponatremia, or hypoalbuminemia, may be not clinically relevant and need to be searched with specific testing.

The diagnosis of KD was made within the sixth day of fever in both groups. As reported by others, the time of diagnosis did not differ in the two groups [1, 4, 10, 18].

Despite the fact that shock symptoms are quite uncommon in KD, which can make diagnosis difficult especially if the shock is at the onset of disease, all our patients with KSS had a timely diagnosis. The timeliness of the diagnosis can be associated both with our patients being treated in pediatric tertiary care centers and since the majority of them had a classical form of disease.

As reported by Gatterre et al. and Zulian et al. [18, 19], we found an association of more severe gastrointestinal manifestations and KSS, maybe related to a more intense systemic vasculitis in patients with KSS than in those with KD. In our series, one patient with KSS underwent a surgical intervention as a result of a clinical and radiologic diagnosis of appendicitis, but postoperative findings were positive for thickening of the ileal loops, consistent with mesenteric vasculitis.

As already reported by others [1, 2, 8, 18], subjects with KSS had higher laboratory inflammatory markers compared with control patients, have CRP levels more than threefold higher, have lower hemoglobin levels, and have more frequently hyponatremia and hypoalbuminemia. Of note is also the more frequent elevation of markers of myocardial damage (cardiac troponins and CPK-MB) in children with KSS, present in 80 % of cases compared to 5 % of controls.

The etiology of KSS is unknown, but clinical and laboratory findings suggest greater underlying inflammation with a more intense systemic vasculitis and more profound myocardial involvement. In our study, we found a significantly higher number of KSS patients with echocardiographic involvement, defined as coronary artery abnormalities, lucency of the wall, and cardiac dilatation in the acute phase of the disease, as already reported [1, 2, 8, 18], but not a higher rate of severe cardiac involvement.

We also noticed that patients with KSS have frequently a reduced ejection fraction, areas of dyskinesia, and areas of infarction or ischemia. Sixty percent of cases presented coronary artery abnormalities compared with 22 % of control patients, but none had permanent coronary aneurysms. Most cardiovascular abnormalities resolved promptly with therapy during the subacute or convalescent phase, and interestingly, no patient presented persistent coronary involvement. This could be explained by the fact that the presence of a more intense inflammation consisted in a sort of "inflammatory myocarditis" rather than a simple coronaritis, giving a justification for the cardiac shock syndrome.

As already reported [2, 8], patients with KSS exhibited more often resistance to IVIG, requiring a second IVIG dose in addition to corticosteroids; at the same time, the KSS patients presented elevated CRP levels, which are considered a predictor of IVIG resistance [20]. The additional treatment given to patients with KSS including vasoactive agents, ventilatory support, and ICU admission emphasize the severity of this complication.

Based on the fact that we do not yet have clinical or biological markers to identify children at increased risk of coronary artery aneurysms or of IVIG resistance [21], and since it has been suggested that administration of intravenous methylprednisolone with first IVIG infusion could be effective for those patients who will not respond to IVIG [22], the early use of steroids together with IVIG could be of benefit. In fact, although the use of steroids is controversial, recent findings have suggested that it could be protective for coronary abnormalities in patients who fail to respond to the first IVIG

Table 2 Studies describing KSS patients; *m* (IQR) = median (interquartile range)

	KSS patients *N*	Incidence %	Male %	Age in years *m* (IQR)	Days of fever at onset *m* (IQR)	Hospitalization days *m* (IQR)	Gastrointestinal involvement %	FE < 54%	Mitral regurgitation %	Pericardial effusion %	Coronary anomalies %	Persistent aneurysm %	Hb g/dl *m* (IQR)	Platelets $\times 10^3$/mmc *m* (IQR)	PCR mg/dl *m* (IQR)	IVIG resistance %
Dominguez et al. [4]	14	3.3	43	3.7 (0.3–10.9)	6.5 (3–16)	8 (5–15)	–	31	–	–	43	29	–	259 (+/−126)	23.8 (+/−15)	64.3
Kanegaye et al. [1]	13	7	31	2.8 (2.2–5.9)	5 (5–6.5)	–	–	–	39	–	61	15	8.9 (7.5–10.1)	148 (97–302)	18.4 (8.7–22)	46
Gatterre et al. [18]	11	–	58.2	6.3 (0.5–14.6)	6 (5–8)	6 (4–11)	69	72.7	18.2	45.5	63.6	0	–	212 (58–449)	31.8 (25.9–43)	36.4
Gámez-González et al. [10]	11	5	73	5.1 (3.5–10.0)	10 (2–23)	–	73	–	–	27	58	27.3	–	–	–	54.5
Our study	5	5.9	80	2.1 (0.4–11.6)	6 (5–6)	10 (8–14)	60	60	20	40	60	0	8.1 (7.1–9.5)	173 (83–500)	27.8 (23.3–96)	60

infusion [23] and that steroids combined with the conventional regimen of IVIG as an initial treatment strategy could reduce the risk of coronary abnormality [24]. In particular, it seems of great interest that steroids could protect from coronary artery abnormalities in patients with severe KD [25].

We noticed that our patients with KSS had better long-term outcomes than those reported in literature [1, 2, 8]. The more favorable prognosis of these patients may be related to early diagnosis, which results in a timely treatment despite increased incidence of IVIG resistance, suggesting that the prompt recognition of KSS and appropriate treatment may reduce the occurrence of coronary artery aneurysms.

Comparison between our study and previous articles is reported in Table 2.

In conclusion, KSS is a rare manifestation of KD and can be the first presentation of KD.

The diagnosis can be difficult, especially if this manifestation occurs in incomplete forms of KD. The diagnosis and treatment of patients with KD depend on awareness of the full spectrum of the disease presentation. We have to remember that shock can be a manifestation of KD and have to keep in mind KD when evaluating patients with shock and associated elevated inflammatory markers with no evidence of infection and/or lack of response to antibiotic treatment. In this subset of patients, in particular, it is important to search for possibly less frequent clinical manifestations. In our experience, clinical outcome was good. However, diagnosis must be suspected early and treatment promptly initiated in order to ensure a good prognosis.

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Compliance with ethical standards

Disclosures None.

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