Kawasaki Shock Syndrome Complicating a Recurrence of Kawasaki Disease

**abstract**

We describe a case of recurrent Kawasaki disease (KD) in a non-Asian 6-year-old boy who had been diagnosed with typical KD without cardiac involvement at age 3 years. He was admitted to the PICU 3 years later for heart failure, hypotension, and deterioration of his general condition. Ultrasonography revealed left ventricular dysfunction with a 44% ejection fraction and grade I mitral valve failure without coronary artery involvement. Subsequent observation of hyperemic conjunctiva, bilateral cervical adenopathies with erythematous skin (normal neck ultrasound and computed axial tomography findings), peeling of the fingertips at day 8 of the illness, and occurrence of an inflammatory syndrome led to a diagnosis of incomplete recurrent KD with a clinical picture of Kawasaki shock syndrome (KSS). Clinical improvement was rapidly obtained after intravenous immunoglobulin and intravenous corticosteroid therapy (30 mg/kg per day for 3 subsequent days). Left ventricular function gradually improved, with ultrasound returning to normal after 3 months. Diagnosis was difficult to establish because of the recurrence of the disease and the incomplete clinical picture, with clinical features of KSS. Physicians need to be aware of these pitfalls in the management of patients with clinical signs of KD. *Pediatrics* 2014;134:e1695–e1699

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**KEY WORDS**
mucocutaneous lymph node syndrome, mucocutaneous lymph node syndrome/therapy, mucocutaneous lymph node syndrome/diagnosis, recurrence, shock/diagnosis, glucocorticoids/therapeutic use, drug therapy/combination, case report

**ABBREVIATIONS**
CRP—C-reactive protein
IVIG—intravenous γ-globulin
KD—Kawasaki disease
KSS—Kawasaki shock syndrome

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Kawasaki disease (KD) is an acute, self-limited vasculitis. Its origin is still unknown despite intensive research. It affects children, mainly between the ages of 6 months and 5 years. Its diagnosis relies on the compilation of clinical and biological data, because no specific diagnostic test exists. Diagnosis must be made early to avoid coronary involvement, which is the most severe complication of KD. The disease can sometimes display atypical or incomplete clinical pictures that the physician needs to know. Also, the disease is liable to recur many months after a first episode.

PATIENT PRESENTATION

At age 3 years, our patient had developed typical KD (fever >5 days, erythema, cheilitis, conjunctivitis, and cervical adenopathies) with a biological inflammatory syndrome (C-reactive protein [CRP]: 18.3 mg/dL; erythrocyte sedimentation rate: 64 mm). Investigations for infection (throat swab polymerase chain reaction analysis for herpes, blood cultures, and serology for mycoplasmas and herpes virus) were negative. Echocardiography on day 6 was normal (telediastolic left ventricle diameter: 35 mm; shortening fraction: 34%; ejection fraction: 65%; no valvular involvement, no coronary abnormalities, and no pericardial effusion). He was treated with intravenous γ-globulin (IVIg, Tegeline, LFB Biomédicaments, Les Ulis, Essonne, France) 2 g/kg on day 5 and acetylsalicylic acid (80 mg/kg per day for 2 weeks and then 3 mg/kg per day for 1 month), and his clinical condition improved rapidly. A diminution of blood pressure occurred during the injection, and was considered to be an anaphylactic reaction. Follow-up echocardiograms at 1 and 3 months were normal.

Three years later, he was again admitted to the PICU for clinical signs of hemodynamic failure (tachycardia: 140 beats per minute; gallop rhythm, hepatomegaly, hypotension with arterial systolic pressure of 70 mm Hg, and edema of the lower limbs), a 4-day history of fever, asthenia, and irritability. On admission, the patient was afebrile; he had hyperemic conjunctiva, abdominal pains, cheilitis, and neck pains with unilateral cervical adenopathies and an erythematous appearance of the skin on the left side of his neck. For 3 days he had been taking cefpodoxime and niflumic acid for a throat infection. Laboratory results were as follows: CRP, 18.2 mg/dL; natremia, 135 mmol/L; neutrophils, 25 Giga/L; platelets, 293 Giga/L; alanine aminotransferase, 277 IU/L; aspartate aminotransferase, 140 IU/L; total bilirubin, 13.68 pmol/L; N-terminal Brain Natriuretic Peptid, 2560 pmol/L; and cardiac I Troponin <0.15 ng/mL. On echocardiography, the left ventricle appeared dilated and hypokinetic, with a 49% ejection fraction, grade I mitral valve failure, and normal coronary arteries and pericardium (Fig 1 A and B). An abdominal ultrasound was performed and revealed hydrocholycystis.

Working diagnoses were either ear-nose-throat infection complicated by cutaneous cellulitis with left ventricular dysfunction after microbial toxin–induced inflammation, or viral myocarditis, or recurrence of KD. Neck ultrasound and computed axial tomography revealed no evidence of any abscess. Blood cultures, skin culture, and blood tests for Epstein-Barr virus, cytomegalovirus, parvovirus B19, toxoplasmosis, and enterovirus were negative. The patient was treated with furosemide 2 mg/kg per day and spirunolactone 2 mg/kg per day, intravenous antibiotics (amoxicillin and clavulanic acid, clindamycin), and aspirin 50 mg/kg per day. Given the history of anaphylaxis and because diagnosis was still uncertain, IVIG was not administrated initially.

On day 8 (the fourth day of hospitalization), the patient developed peeling skin on the fingers, which prompted the diagnosis of Kawasaki shock syndrome (KSS). Inflammatory parameters were as follows: CRP, 25.5 mg/dL; white blood cell count, 18.53 Giga/L; and neutrophils, 12.5 G/L. Treatment with IVIG (Gammagard (Baxter, Lessines, Belgium) 1 g/kg per day for 2 days to avoid vascular overload) and intravenous corticosteroids (methylprednisolone 30 mg/kg per day for 3 days) was initiated on the same day. There was no need for inotropic support. The patient’s clinical status rapidly improved, with resolution of the signs of heart failure and abdominal pain, regression of the biological inflammatory syndrome, and improvement in echocardiogram findings (Fig 1 C and D). Thrombocytosis (529 G/L) appeared on day 10. Diuretics were discontinued on day 17. Aspirin was maintained at antiinflammatory doses for 15 days, and then at a platelet aggregation–inhibiting dose for 1 month.

Two months and 1 year after admission, the cardiac examination and ultrasound results were in the normal range (left ventricular ejection fraction of 65%).

DISCUSSION

Our patient first presented a clinical picture of complete KD followed by a quick recovery after IVIG. The second bout of the disease was less typical because of the prevalent hemodynamic features. The diagnosis of KD was finally made after suggestive clinical pictures appeared and was confirmed by the rapid improvement after IVIG.

The diagnosis of KD is made according to the criteria of the American Heart Association. In 20% of cases, the clinical presentation is incomplete or challenged by predominant atypical manifestations (cranial nerve palsies, acute abdomen, massive lymphadenopathy, meningitis, encephalitis, aseptic meningitides, uveitis, pancreatitis, pneumonitis, etc), and cardiac ultrasonography and biological criteria are required to establish diagnosis.3

In ~ 7% of cases the clinical picture of KD mimics a toxic shock syndrome, most commonly with hypotension, termed KSS.3 The shock may be distributive or cardiogenic in origin, or both. KSS is characterized by more atypical presentation, more
coronary artery involvement and resistance to IVIG, and more severe biological inflammatory syndrome in comparison to KD.4 Overall, KSS resembles a severe form of KD, in the acute phase and in terms of coronary risk, with an exacerbated inflammatory and immune reaction. Recurrence of KD is defined by the recurrence of symptoms > 2 months after the first episode.5 Cases of recurrent KD are rare in Europe, and so we have no relevant epidemiologic data. Relapses have been reported in Japan,6 China,7 Taiwan,8 Korea,9 and the United States10 at respective rates of 3%, 3.5%, 1.82%, 1.5%, and 0.8%. The disease seems to recur more frequently in the first 2 years after diagnosis, with the highest rates between the ages of 1 and 2 years, and with a lower risk in children aged ≥ 3 years at initial onset.5,6,11,12 In our case, the clinical presentation was incomplete, with, in particular, a febrile episode lasting only 4 days. In the case of recurrent KD, the fever duration has been reported to be shorter,13,14 but overall clinical features and response to IGIV are comparable in single-episode and recurrent KD.12,15 Whether recurrent KD has more coronary sequelae is not clear.12,15,16,17 Taken together, these data do not reveal any salient differences in clinical features between single-attack and recurrence of KD. The recurrence of KD seems to be a repetition of the same self-limited inflammatory process in persons genetically prone to developing the disease. Table 1 compares the mean clinical features and outcomes of recurrent KD, KSS, and our case.

In the case we describe here, the recurrence was strikingly more severe than the first attack. A widespread theory of the etiology of KD states that ≥ 1 widely distributed infectious agents triggers an abnormal immunologic response in genetically susceptible persons. In our reported case, the recurrence of the disease could reflect a genetic susceptibility to developing KD, whereas the different severity (between the 2 attacks) suggests the role of additional environmental factors. In our case, abdominal pains occurred in the second episode, but not during the first one. These abdominal signs resolved with the IVIG treatment. Gámez-González et al4 emphasized the high frequency of gastrointestinal manifestations in patients with KSS (up to 73%). Gastrointestinal tract involvement has proved a poor prognosis factor in other vasculitis.18 Overall, abdominal signs could reflect one of the mechanisms through gut bacteria superantigens19 or cytokine release from an involved gut. However, it could also be the consequence of hemodynamic failure through mesenteric ischemia.

Given the recurrent nature of the disease, the clinical picture (KSS),4 and the observed risk factors (alanine aminotransferase > 80 IU/L; CRP > 8 mg/dL; platelets < 300 Giga/L; Egami score, which identifies patients with a high risk of vascular complications, > 320), the patient was at high risk of vascular complications, and so we considered that combined corticosteroid and IVIG therapy was indicated. There are no official guidelines for the treatment of recurrent KD, but there is evidence that adjuvant corticosteroid and IVIG therapy decreases the risk of vascular lesions,21 particularly in patients prone to such a risk.22

In our observation, the recurrence appeared at age 6 years, with a clinical picture of myocardial involvement. In
a series of 4 cases of KD with myocardial involvement reported by Yoshikawa et al,\textsuperscript{23} 3 of the patients were aged $\geq 6$ years.

Our patient's symptoms rapidly improved after treatment with IVIG. In the study by Moran et al,\textsuperscript{24} two-thirds of patients receiving IVIG (of whom 93% had myocardial impairment at diagnosis) showed improvement in myocardial function from the third day of treatment. In addition, Newburger et al\textsuperscript{25} showed that patients with myocardial impairment improved their myocardial function with IVIG more rapidly than with aspirin alone.

**CONCLUSIONS**

We report a case of recurrent KD presenting as KSS. The rarity of recurrence and our patient's atypical clinical presentation made diagnosis difficult. The major challenge of KD is diagnosing and treating it before irreversible coronary damage appears. Both of the 2 pitfalls reported in our case (ie, KSS and recurrences) need to be made known to pediatricians. In the case of risk factors for coronary involvement, treatment by intravenous corticosteroids must be considered.

### REFERENCES


**TABLE 1** Clinical Features, Vascular Involvement, and IVIG Resistance in Case-Control Studies Comparing KSS With KD, Case-Control Studies Comparing Recurrent KD With Nonrelapsing KD, and Our Reported Case

<table>
<thead>
<tr>
<th></th>
<th>KSS Versus KD Without Nonrelapsing KD (1650 patients)</th>
<th>Recurrent KD Versus Relapse Versus First Attack</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case-control studies</td>
<td>Kanegaye et al\textsuperscript{26}</td>
<td>Nakamura et al\textsuperscript{17}</td>
</tr>
<tr>
<td>Gámez-González et al\textsuperscript{4}</td>
<td>Nakamura\textsuperscript{16}</td>
<td>Chahal et al\textsuperscript{15}</td>
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<tr>
<td>Chen et al\textsuperscript{27}</td>
<td>Yang et al\textsuperscript{12}</td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>More incomplete presentation</td>
<td>Similar symptoms</td>
</tr>
<tr>
<td></td>
<td>More abdominal pains</td>
<td></td>
</tr>
<tr>
<td>Laboratory data</td>
<td>More elevated CRP</td>
<td>No differences</td>
</tr>
<tr>
<td></td>
<td>Lower platelet count</td>
<td>Platelet count in normal range</td>
</tr>
<tr>
<td>Vascular involvement</td>
<td>More coronary involvement\textsuperscript{16,17}</td>
<td>No coronary involvement</td>
</tr>
<tr>
<td></td>
<td>Similar coronary involvement\textsuperscript{12,15}</td>
<td></td>
</tr>
<tr>
<td>IVIG resistance</td>
<td>More IVIG resistance</td>
<td>No differences</td>
</tr>
</tbody>
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\textsuperscript{a} The reported case was treated at once as IVIG-resistant KD.

\textsuperscript{b} The data presented in this column are solely our data.


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