Early Differentiation of Kawasaki Disease Shock Syndrome and Toxic Shock Syndrome in a Pediatric Intensive Care Unit

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Background: Kawasaki disease shock syndrome (KDSS) and toxic shock syndrome (TSS) can present as shock and fever with skin rash, but the management of these 2 groups of patients is different. This report proposes to help clinicians earlier distinguish these 2 diseases and expedite institution of appropriate therapy.

Methods: We retrospectively reviewed the medical records of patients admitted to the pediatric intensive care unit with the diagnosis of KDSS or TSS from January 2000 through December 2010. Clinical, laboratory and echocardiographic data were collected for analysis of differences between them.

Results: Seventeen patients met the inclusion criteria of KDSS and 16 had a confirmed diagnosis of TSS. The mean age of the KDSS group was significantly younger than that of the TSS group (36.8 ± 41.1 vs. 113.3 ± 55.6 months, P < 0.001). Significantly lower hemoglobin and age-adjusted hemoglobin concentrations were noted in the KDSS group [Hb, age-adjusted Z score, −1.88 (range, −3.9 to 3.9) vs. 0.89 (range, −6.4 to 10.8), P = 0.006]. The median platelet count of the KDSS group was nearly twice that of the TSS group [312 × 10^3 per μL (range, 116–518) vs. 184.5 × 10^3 per μL (range: 31–629), P = 0.021]. Echocardiographic abnormalities, such as valvulitis (mitral or tricuspid regurgitation) and coronary artery lesions, were significantly more common in the KDSS group (P = 0.022).

Conclusions: Echocardiography, anemia and thrombocytosis are useful early differentiating features between KDSS and TSS patients.

Key Words: Kawasaki disease shock syndrome, toxic shock syndrome, echocardiography, anemia, thrombocytosis

(Kawasaki disease (KD), also known as acute febrile mucocutaneous lymph node syndrome, is a pediatric condition consisting of an acute systemic inflammatory vasculitis. KD is a significant risk factor for coronary artery damage, with 25% of untreated patients developing lifelong coronary artery lesion (CAL). KD is, therefore, recognized as a leading cause of acquired heart disease, particularly in East Asia. Intravenous immunoglobulin (IVIG) therapy has dramatically decreased the incidence of CAL and has, therefore, lowered the mortality rate associated with KD. The clinical manifestation of KD varies, and patients may not completely fulfill all criteria of KD, a clinical diagnosis known as “incomplete or atypical” KD. Although uncommon, patients with KD may also present with hypotension or shock. This is a severe form of KD known as “Kawasaki disease shock syndrome” (KDSS), which requires hemodynamic support and intensive medical care.

Differentiating between KDSS and toxic shock syndrome (TSS) in the early stages of clinical diagnosis is challenging. TSS is an acute, exotoxin-mediated, multisystem disease caused by superantigens of Staphylococcus aureus or Streptococcus pyogenes. The presenting clinical features of TSS include fever, a rash, hypotension, multisystem involvement and desquamation. Although the clinical presentation of TSS is comparable with that of KDSS, the clinical management is quite different, with patients with TSS requiring appropriate antimicrobial therapy to eradicate the bacteria and neutralized toxin, in addition to aggressive fluid resuscitation and vasopressors for hemodynamic stabilization. In contrast, for patients with KDSS, antibiotics are not necessary, but IVIG therapy and follow-up echocardiography are important because of the potential for CAL formation.

As the clinical presentation of KDSS and TSS is similar with shock, fever and skin rash, identification of clinical variables with sufficient sensitivity and specificity is required to assist clinicians in pediatric intensive care units (PICU) to reliably differentiate between these 2 conditions in the early phase of clinical diagnosis. Therefore, we conducted a retrospective analysis of medical records of patients admitted to our institutional PICU with a diagnosis of KDSS or TSS to evaluate differences in clinical, laboratory and echocardiographic data that would differentiate between these 2 groups of patients.

MATERIALS AND METHODS

Patients

The medical records of patients admitted to the PICU at Kaohsiung Chang Gung Memorial Hospital, with the diagnosis of KDSS or TSS from January 2000 to December 2010, were reviewed. All patients were younger than 18 years of age. The study protocol was approved by our Institutional Review Committee on Human Research.

Diagnosis of KD was based on the presence of a fever lasting at least 5 days, in combination with at least 4 of the following 5 clinical features typical of KD: bilateral bulbar conjunctival injection, oral mucous membrane changes, peripheral extremity changes, polymorphous rash and cervical lymphadenopathy. A diagnosis of incomplete or atypical KD was used for patients with a history of fever lasting more than 5 days, presenting with less than 4 of the clinical features typical of KD but showing evidence of CAL on echocardiography.

All patients with TSS were diagnosed by infection specialists using the diagnostic criteria for staphylococcal or streptococcal infection described below.

1. TSS caused by staphylococcal infection includes fever, rash, desquamation, hypotension and involvement of 3 or more systems—gastrointestinal, mucosal, renal, hepatic, hematological or central nervous system.

2. TSS caused by streptococcal infection includes isolation of group A β-hemolytic streptococci from sterile or nonsterile site, hypotension and 2 or more of the following clinical signs—renal impairment, coagulopathy, hepatic involvement, acute respiratory distress syndrome, skin rash with possible desquamation and soft tissue necrosis.
Shock was defined primarily by systemic hypotension, with the following age-specific cutoffs used: infants aged <1 month, systolic blood pressure (SBP) <60 mm Hg; infants aged 1–12 months, SBP <70 mm Hg; children aged 1–10 years, SBP <70 + (age × 2) mm Hg and children aged >10 years, SBP ≥90 mm Hg. Other clinical signs of shock included tachycardia, prolonged capillary refusion, mental status changes or oliguria. Hypotension remains a cardinal sign for well-trained physician to initiate volume expansion, inotropic agent use and care in intensive care unit.6

Clinical and Laboratory Data

The following data were retrospectively extracted from the medical chart: patient-specific demographic and clinical information, results of laboratory test obtained immediately before or after admission to the PICU; details on the clinical management of shock, including amount of volume expansion and dosage of inotropic agent administered, and clinical outcome. Because of the dependence of hemoglobulin (Hb) concentration on age,12 Hb concentrations were corrected for age as follows: ([observed Hb] − [mean Hb for age])/standard deviation of Hb for age).13

Echocardiography

Echocardiographic assessment was performed using a Hewlett-Packard/Philips Sonos Ultrasound machine (models 5500 and 7500), using the following imaging protocol: M-mode, 2-dimensional, pulsed-wave, continuous-wave, and color Doppler imaging. All echocardiograms were evaluated by more than 1 pediatric cardiologist in a blinded manner.

With high-quality ultrasound imaging machines, valve regurgitation can be identified by echocardiography. Therefore, the severity of valve regurgitation was graded from standard colorflow Doppler imaging, using the semiquantitative categories of the Framingham Heart Study criteria: "none," "trace," "mild," "moderate," and "severe," as shown in Table 1.14,15 Significant valve regurgitation was defined by the following grade cutoffs: a grade above "moderate" for tricuspid valve regurgitation (TR) and above "mild" for mitral valve regurgitation (MR). Valvulitis was similarly defined by a cut-off grade above "moderate" for TR and "mild" for MR or any degree of aortic valve regurgitation.

CAL was defined using the criteria from the traditional Japanese Ministry of Health, which include a maximum absolute intern diameter >3 mm in children younger than 5 years, or >4 mm in children 5 years and older, a segment with a diameter 1.5 times greater than that of an adjacent segment and/or the presence of luminal irregularity.16,17 More recently, the definition of CAL has been modified, with CAL defined by a Z score ≥2.5, corrected for body surface.18 Both criteria for CAL identification were used in our analysis, as earlier charts did not report the height measurement necessary for the calculation of body surface area. Left ventricular (LV) dysfunction was defined as a shortening of the LV fraction <28% and an associated lowering of the ejection fraction to <54%.

### Statistics

Significant differences in the median values for continuous variables were evaluated using a 2-tailed Mann–Whitney U test, whereas differences in means were evaluated using 2-tailed Student’s t test. Categorical variables were compared using Fisher exact test. All analyses were performed using the Statistical Package for the Social Sciences version 18.0 (SPSS, Chicago, IL). The statistical significance level was set at $P < 0.05$.

### RESULTS

Between January 2000 and December 2010, 25 patients were admitted to the PICU with a confirmed diagnosis of KD on discharge. Of these patients, 17 (68%) met the inclusion criteria for KDSS and were enrolled into the study. Over the same time frame, 16 were admitted with a diagnosis of TSS confirmed by infection specialists; these patients were enrolled into the study.

There were no significant between-group differences for patients in the KDSS and TSS groups in terms of sex-distribution, initial presentation at intensive care unit admission or mortality rate. However, the groups did differ on specific variables (Table 2). Patients in the KDSS group were significantly younger, with a mean age of 36.8 ± 41.1 months compared with 113.3 ± 55.6 months for the patients in the TSS group ($P < 0.001$). Patients in the TSS group required higher fluid expansion amounts and dopamine dosages to maintain blood pressure than patients in the KDSS group, 10.9 ± 18.3 mL/kg compared with 29.7 ± 32.6 mL/kg for fluid expansion amounts ($P = 0.048$) and 7.3 ± 5.5 μg/kg/min compared with 12.3 ± 7.5 μg/kg/min for dopamine dosage ($P = 0.035$). Patients in the KDSS group had significantly lower absolute and age-adjusted Hb concentrations compared with patients in the TSS group, with a mean Z score of age-adjusted Hb concentration of −1.88 (range, −3.9 to 3.9) for the KDSS group and −6.4 to 10.8 for the TSS group ($P = 0.006$). Median platelet count of the KDSS group was nearly twice that of the TSS group [312 ± 103 per μL (range, 116–518) vs. 184.5 ± 103 per μL (range, 31–629), $P = 0.021$]. No significant between-group differences were identified for white blood cell count, polymorphonuclear neutrophil (PMN) count and percentage or percentage of band form neutrophil (Table 3).

The creatinine level of the TSS group was higher than that of the KDSS group [1.53 mg/dL (range, 0.5–3.89) vs. 0.45 mg/dL (range, 0.3–1.8), $P = 0.001$]. Although both erythrocyte sedimentation rates and C-reactive protein levels were elevated in these 2 groups, most of these acute-phase proteins were not significantly different between the groups.

### TABLE 2. Demographics and Clinical Characteristics of KDSS and TSS Groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>KDSS (n = 17)</th>
<th>TSS (n = 16)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD (mo)</td>
<td>36.8 ± 41.1</td>
<td>113.3 ± 55.6</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>11 (65)</td>
<td>9 (56)</td>
<td>0.728</td>
</tr>
<tr>
<td>Initial admission to ICU, n (%)</td>
<td>4 (24)</td>
<td>9 (56)</td>
<td>0.08</td>
</tr>
<tr>
<td>Total fluid challenge volume (mL/kg)</td>
<td>10.9 ± 18.3</td>
<td>29.7 ± 32.6</td>
<td>0.048</td>
</tr>
<tr>
<td>Maximal dopamine dose (μg/kg/min)</td>
<td>7.3 ± 5.5</td>
<td>12.3 ± 7.5</td>
<td>0.035</td>
</tr>
<tr>
<td>Maximal dobutamine dose (μg/kg/min)</td>
<td>1.4 ± 4.2</td>
<td>4.38 ± 7.3</td>
<td>0.169</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>0 (0)</td>
<td>2 (13)</td>
<td>0.227</td>
</tr>
</tbody>
</table>

Bold values are statistically significant.

SD indicates standard deviation; ICU, intensive care unit.
there were no statistically significant differences between them. Additionally, there were no differences in liver function and albumin and troponin I levels between these 2 groups (Table 4).

All 17 patients in the KDSS group and 7 of the 16 patients in the TSS group received an echocardiographic assessment within the first 24 hours of being admitted to the PICU. Significant TR was identified in 7 children from the KDSS group (41%) and MR in 6 children (35.3%). Significant MR and TR were not identified in patients in the TSS group. Although there was no statistical difference in the incidence of individual MR and TR between these 2 groups, valvulitis was significantly more common in the KDSS group compared with the TSS group (P = 0.022). LV dysfunction and pericardial effusion were more common in the KDSS group, but the between-group difference in incidence did not reach statistical significance. CAL was a significantly more common finding in patients in the KDSS group (P = 0.022; Table 5).

### DISCUSSION

In spite of “theoretically” well-defined clinical and biological criteria, there is considerable overlap in the clinical features of TSS and KDSS, which makes differential diagnosis in practice difficult.19-23 Therefore, we conducted a retrospective medical chart review to compare and contrast the clinical features of patients with KDSS and TSS, with the aim of identifying specific features that would inform early differential diagnosis between these 2 conditions.

According to the Nelson Text Book of Pediatrics, 80% of patients with KD are younger than 5 years of age, with the typical median age at the time of presentation being 2–3 years. In contrast, patients presenting with TSS group tend to be older (Table 2). However, KDSS has been described in patients over the entire age range of pediatrics,1 and even in adult patients.19,26-28 Therefore, age does not provide a specific criterion for the differential diagnosis of KDSS from TSS, and consequently, other clinical features or parameters are required to reliably differentiate these 2 conditions.

Laboratory studies are essential to identify severe cases of KDSS. In our series, hypoaalbuminemia was identified in 12 of the 17 patients with a clinical diagnosis of KDSS. Dominguez et al29 reported significantly lower albumin in children admitted to PICU with KDSS, compared with a control pediatric population, indicating a possible correlation between albumin and increased vascular permeability.

Gatterer et al30 hypothesized that the “overexpression” of proinflammatory cytokines, in combination with an intense and systemic inflammation, leads to multiple organ damage and failure in KDSS. In our study group, initial creatinine levels were significantly higher in the TSS group. As well, patients in the TSS group needed higher amounts of fluid expansion and dosages of inotropic agents to maintain blood pressure. Two patients from the TSS group died; however, no mortality was reported for the KDSS group. We hypothesize that in cases of severe KDSS, timely administration of IVIG therapy leads to rapid and effective neutralization of the life-threatening inflammation.

Although the underlying mechanism of anemia in KDSS is still unclear, hemolytic anemia in patients with KDSS has been reported in the literature. Recently, Kuo et al31 reported an inflammation-induced downregulation of hepcidin, which has been associated with the development of anemia in patients with KDSS. Patients with KDSS in our study tended to have anemia, including low, age-adjusted, Z scores of Hb concentration. In contrast, anemia has not been reported in TSS. Thrombocytopenia is a diagnostic criterion of TSS, and thrombocytopenia might also develop in KDSS. In our study group, platelet count was significantly higher in the KDSS group. However, platelet counts in these patients were still within the accepted “normal” range, and therefore, reliable cut-off levels for differential diagnosis between KDSS and TSS could not be defined.32,33 The absence of a clear diagnostic criterion based on platelet count is corroborated by previous studies, which have reported an inconsistent association between thrombocytopenia or thrombocytopenia and KDSS. As an example, although Kanegaye et al34 reported significantly lower platelet counts in 13 patients with KDSS (148 × 10³ per µL) compared with patients with KD without shock (410 × 10³ per µL), 4 patients in their study group had a normal platelet count before IVIG therapy, and the level for 2 other patients were not reported. In the case-control study by Dominguez et al,29 the lowest platelet count reported in a group

### TABLE 3. Laboratory Data of KDSS and TSS Groups

<table>
<thead>
<tr>
<th>Tests</th>
<th>KDSS (n = 17), median (range)</th>
<th>TSS (n = 16), median (range)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC count (10³/µL)</td>
<td>14.6 (0.5 to 20.6)</td>
<td>17.3 (0.45 to 39.2)</td>
<td>0.471</td>
</tr>
<tr>
<td>PMN count (10³/µL)</td>
<td>11.55 (2.11 to 17.3)</td>
<td>14.4 (3.33 to 34.50)</td>
<td>0.564</td>
</tr>
<tr>
<td>PMNs (%)</td>
<td>79.4 (37 to 95)</td>
<td>78.6 (54 to 96)</td>
<td>0.843</td>
</tr>
<tr>
<td>Bands (%)</td>
<td>0 (0 to 15)</td>
<td>0.5 (0 to 30)</td>
<td>0.229</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>10 (7.9 to 13.8)</td>
<td>13.7 (8.3 to 18.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hb, age-adjusted Z score</td>
<td>−1.88 (−3.9 to 3.9)</td>
<td>0.89 (−6.4 to 10.4)</td>
<td>0.006</td>
</tr>
<tr>
<td>Platelet count (10³/µL)</td>
<td>312 (116 to 518)</td>
<td>184.5 (31 to 629)</td>
<td>0.021</td>
</tr>
</tbody>
</table>

Bold values are statistically significant.

WBC indicates white blood cell; PMN, polymorphonuclear neutrophil.

### TABLE 4. Biochemical Laboratory Values of KDSS and TSS Groups

<table>
<thead>
<tr>
<th>Tests</th>
<th>KDSS (n = 17), median (range)</th>
<th>TSS (n = 7), median (range)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR (mm/h)</td>
<td>9.55 (21–127)</td>
<td>3.72 (23–111)</td>
<td>0.643</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>17, 164.8 (70–352.2)</td>
<td>16, 135 (0.3–367.1)</td>
<td>0.829</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>16, 9 (4–40)</td>
<td>14, 23.5 (6–58)</td>
<td>0.139</td>
</tr>
<tr>
<td>Cr (mg/dL)</td>
<td>16, 0.45 (0.3–1.8)</td>
<td>14, 1.53 (0.5–3.89)</td>
<td>0.001</td>
</tr>
<tr>
<td>AST (UL)</td>
<td>16, 46.5 (20–388)</td>
<td>15, 50 (27–307)</td>
<td>0.44</td>
</tr>
<tr>
<td>ALT (UL)</td>
<td>16, 60 (8–311)</td>
<td>15, 47 (10–206)</td>
<td>0.477</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>12, 2.45 (1.6–3.0)</td>
<td>13, 2.5 (1.7–3.5)</td>
<td>0.126</td>
</tr>
<tr>
<td>Prothrombin</td>
<td>9, 0.08 (0–0.9)</td>
<td>7, 0.3 (0.05–1.8)</td>
<td>0.339</td>
</tr>
</tbody>
</table>

Bold values are statistically significant.

ESR indicates erythrocyte sedimentation rate; CRP, C-reactive protein; BUN, blood urea nitrogen; Cr, creatinine; AST, aspartate aminotransferase; ALT, alanine transaminase.

### TABLE 5. Echocardiography of KDSS and TSS Groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>KDSS (n = 17), n (%)</th>
<th>TSS (n = 7), n (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitral regurgitation ≥ mild</td>
<td>7 (41.2)</td>
<td>0 (0)</td>
<td>0.065</td>
</tr>
<tr>
<td>Tricuspid regurgitation ≥ moderate</td>
<td>6 (35.3)</td>
<td>0 (0)</td>
<td>0.130</td>
</tr>
<tr>
<td>Valvulitis*</td>
<td>9 (52.9)</td>
<td>0 (0)</td>
<td>0.022</td>
</tr>
<tr>
<td>Impaired LV performance</td>
<td>6 (35.3)</td>
<td>1 (14.3)</td>
<td>0.625</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>2 (11.8)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Coronary artery lesion</td>
<td>9 (52.9)</td>
<td>0 (0)</td>
<td>0.022</td>
</tr>
</tbody>
</table>

Bold values are statistically significant.

*Valvulitis was defined by a cut-off grade above “moderate” for TR and “mild” for MR, or any degree of aortic valve regurgitation.
of 14 with KDSS was also within “normal” limits at 220 × 10^9 per µL. Recently, Fang et al. and Gámez-González et al. also reported inconsistent findings of thrombocytopenia in patients with KDSS. Thabet et al. described the case presentation for a 5-month-old female infant with KDSS, with results of routine laboratory tests reported during the first 7 days of admission to the PICU. Initial platelet count, repeated twice during the first day of admission, was within normal limits and subsequently dropped after the first day following admission. The general conditions and hemodynamic state of this infant improved over the following 24–72 hours after administration of immunoglobulin infusion (1 g/kg for 2 days intravenous). Improvements included normalization of her renal function, coagulation profile, white blood cell count, Hb concentration and platelet count, as well as improvements on other inflammatory markers. Therefore, timely implementation of IVIG therapy is effective in curtailing the inflammatory process and the associated thrombocytopenia.

The causes and factors contributing to the development of shock in KDSS are not entirely clear and are likely to include a specific cardiogenic component, as well as a more general multisystem component. Valvulitis and LV dysfunction have been widely reported in patients with KDSS. Vasculitis, which produces important capillary fragility, including myocardial dysfunction, the release of inflammatory cytokines and increased vascular leakage, may all contribute to the cardiogenic component. Kanegaye et al. reported LV dysfunction and MR to be common findings in patients with KDSS, with an incidence of 31% and 39%, respectively. In their study, Gatattere et al. reported a LV systolic dysfunction [24% (10–28%)] in 8 of their 11 patients with KDSS, with suspected myocarditis being identified in 6 of these 8 patients; the incidence of myocarditis was reported to be likely associated with the elevation in serum cardiac troponin I. We have reported similar findings in our previous study, with a higher incidence of myocarditis and valvulitis in patients with KDSS, compared with patients with TSS. In contrast, the most common initial echocardiographic finding in patients with TSS is hyperdynamic LV performance without myocardium depression, a finding similar to patients presenting with septic shock. This cardiogenic finding in TSS is likely to reflect a compensatory effect to physiological shock, rather than a direct myocardium involvement. Therefore, echocardiography may serve as a sensitive method for early differentiation between KDSS and TSS.

Gámez-González et al. also reported a high incidence of coronary complications associated to KDSS, with 124 of the 214 patients in their study (58%) presenting with coronary artery abnormalities and 82 patients (38%) with coronary aneurysms. Yim et al. reported 2 cases of older children, presenting with features strongly suggestive of TSS, who were ultimately diagnosed with KD after findings of coronary artery abnormalities on echocardiography assessment. Similarly, in our study, we reported a statistically higher incidence of CALs in patients with KDSS than in patients with TSS. In case of clinical doubt, an echocardiography should be performed to assess for valvulitis, myocardial depression or coronary artery involvement. Once a differential diagnosis is established, IVIG therapy for patients with a diagnosis of KDSS and antibiotic therapy, using an agent with antitoxin effect such as clindamycin, in patients with TSS, should be started as soon as possible.

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