Kawasaki Syndrome–Like Illness Associated with Infection Caused by Enterotoxin B–Secreting Staphylococcus aureus

Mary Hall, Laura Hoyt, Patricia Ferrieri, Patrick M. Schlievert, and Hal B. Jenson

Two children had symptoms and clinical signs that were characteristic of the diagnostic criteria for Kawasaki syndrome, temporally associated with Staphylococcus aureus bacteremia. One child initially had focal osteomyelitis that was evident clinically and radiographically, and radiographic evidence of multifocal osteomyelitis was noted at follow-up. The blood-borne S. aureus isolates from these two patients secreted staphylococcal enterotoxin B and were negative for toxic shock syndrome toxin. Staphylococcal and streptococcal superantigens may play a role in the pathogenesis of some cases of Kawasaki syndrome or Kawasaki syndrome–like illness.

Kawasaki syndrome (KS) is an acute systemic vasculitis of early childhood [1, 2]. Although the acute illness is self-limited, coronary artery aneurysms occur in 20%–30% of untreated patients and cause significant morbidity and mortality in affected children. The etiology of KS has been the subject of intense study in recent years but remains unknown. There are similarities between KS and staphylococcal and streptococcal toxic shock syndromes, and it has been proposed that toxins secreted by some strains of Staphylococcus aureus and Streptococcus pyogenes (group A Streptococcus), acting as superantigens, may initiate the intense immune activation characteristic of KS.

In one series, colonization of the skin and mucous membranes with toxin-producing S. aureus and S. pyogenes was found in 13 of 16 patients with KS [3]. The 11 toxin-producing S. aureus isolates secreted toxic shock syndrome toxin-1 (TSST-1). Kawasaki syndrome–like illness has not been reported in association with concurrent focal or systemic S. aureus infection, however. We report on two children with clinical manifestations that were characteristic of the diagnostic criteria for KS, temporally associated with infections caused by enterotoxin B–secreting strains of S. aureus.

Case Reports

Case 1

A 7-month-old boy presented at the emergency department because of a 3-day history of fever (temperatures to 40°C), increasing lethargy, irritability, bilateral lower-extremity swelling and pain, and eyelid-swelling. He had been treated with amoxicillin for presumed otitis media for 2 days, without improvement. His temperature was 38.9°C. The tongue was erythematous with prominent papillae. The lips were hyperemic, dry, and cracked. The conjunctivae were normal. There were marked edema and erythema of the hands and feet and a fine, erythematous, macular rash on the trunk and legs.

Neurological examination revealed profound irritability and minimal spontaneous movement of the lower extremities, with intact sensation and deep tendon reflexes. The remainder of the physical examination, including that of the tympanic membranes, was unremarkable.

Initial laboratory evaluation showed a WBC count of 12.5 × 10³/L (12.5 × 10³/mm³), with 47% neutrophils and 7% band forms. The hematocrit was 26.3%; reticulocyte count, 1.1%; platelet count, 49 × 10³/L (49 × 10³/mm³); and erythrocyte sedimentation rate (ESR), 15 mm/h. Findings with regard to serum electrolytes, calcium, blood urea nitrogen, serum creatinine, hepatic enzymes, creatine phosphokinase, prothrombin and partial thromboplastin times, urinalysis, CSF, and hemoglobin electrophoresis were normal. CT of the head and abdomen and MRI of the spine revealed no abnormalities.

Because of the fever, lethargy, extreme irritability, and thrombocytopenia, the patient was admitted to the hospital and treated with cefotaxime (150 mg/[kg · d]) and oxacillin (200 mg/[kg · d]) intravenously. He remained extremely irritable, with bilateral lower-extremity tenderness. On the third hospital day, a physical examination suggested localized tenderness of the left knee. A ⁹⁹mTc bone scan on hospital day 4 showed focal uptake in the proximal portion of the left tibia, with no uptake at other areas.

The blood culture performed on admission yielded S. aureus susceptible to oxacillin. Osteomyelitis was diagnosed, and treatment with oxacillin alone was continued. Osteomyelitis of the left proximal tibia was confirmed on hospital day 14 by
MRI that showed abnormal intermediate T1-weighted and T2-weighted signal intensities and abnormal enhancement within the left proximal tibial metaphysis, consistent with osteomyelitis. There were similar findings along the periosteum of the tibia and surrounding soft tissues, consistent with periostitis and inflammation of soft tissues, respectively. A small (<1-cm) area of nonenhancement was present in the proximal tibia, consistent with a small abscess or area of bone necrosis. There was no knee-joint effusion.

By hospital day 6 the irritability had gradually improved. A right-knee effusion developed on day 7. Arthrocentesis of the right knee on hospital day 10 revealed a small amount of sterile fluid, with a WBC count of 3.16 × 10⁹/L (3.16 × 10³/µm³). The antinuclear antibody titer was <1:4, and a test for rheumatoid factor was negative. The WBC count was 31.8 × 10⁹/L (31.8 × 10³/µm³) on hospital day 2 and decreased to 12.7 × 10⁹/L (12.7 × 10³/µm³) on hospital day 7. The ESR peaked at 70 mm/h on hospital day 7. Fever (with daily temperatures of >38.9°C) continued through hospital day 10 despite appropriate antipyretic therapy.

On hospital day 13, after the patient had been afebrile and without lower-extremity tenderness for 3 days, the platelet count was 1,800 × 10⁹/L (1,800 × 10³/µm³), and there was periungual desquamation on the fingers and toes. Atypical KS was diagnosed on the basis of the persistence of fever and the occurrence of three of five diagnostic criteria, accompanied by extreme irritability, desquamation, and marked thrombocytopenia. He was treated with intravenous immunoglobulin (2 g/kg) and high-dose aspirin, resulting in clinical resolution of the symptoms and signs of KS.

Two-dimensional echocardiography revealed no coronary abnormalities on hospital day 13 and at 6 weeks after his initial presentation. Plain radiographs on hospital discharge were normal. Four weeks later he presented with decreased movement of the right arm. Plain radiographs at that time showed signs of osteomyelitis (i.e., bone destruction and periosteal elevation) in the left proximal tibia, left proximal humerus, and a rib, consistent with multifocal osteomyelitis. He was treated with a combination of intravenous and oral antibiotics for 6 weeks, and the osteomyelitis and pseudoparalysis of the right arm resolved.

Case 2

A previously healthy 5-year-old boy developed illness initially characterized by fever (temperatures to 40°C), sore throat, headache, and vomiting. On the fourth day of illness he was seen in his primary care clinic and was found to have tonsillar enlargement with a white exudate, and a rapid group A streptococcal antigen test was positive. He was treated with benzathine penicillin G (25,000 U/kg) intramuscularly. Six hours later he presented at the emergency department because of the development of an erythematous maculopapular rash that began in his genital area and spread over his body to include his face and later the palms of his hands. He had a strawberry tongue and erythema of the conjunctivae without discharge.

He was treated with a single dose of vancomycin (10 mg/kg intravenously), methylprednisolone (2 mg/kg intravenously), and diphenhydramine (1 mg/kg intravenously) and was admitted to the hospital for observation. The rash faded but was followed by desquamation over the eyelids and in the genital area. He was diagnosed as having scarlet fever and discharged on the fifth day of illness. No additional antibiotics were prescribed.

Over the next 4 days he had recurrent fever, which was treated with repeated doses of acetaminophen and ibuprofen. He remained anorexic and fatigued and complained of an irritated tongue and a sore right knee. On the eighth day of the illness he had a minor fall on his right knee, followed by marked pain with ambulation.

Evaluation on readmission to the hospital showed minimal limitation of extension of the right knee, but no warmth, erythema, or effusion was noted. Radiographs of the knee and hip were normal. Physical examination was remarkable for a temperature of 39.1°C, nontoxic appearance, erythematous conjunctivae without discharge, hyperemia of the oropharynx, mild nasal crusting, and fine desquamation of skin of the eyelids and in the genital area. It was noted that the blood culture performed 4 days previously, on admission during the first hospitalization, yielded S. aureus on the second day of incubation.

On the ninth day of illness the significant laboratory findings included a WBC count of 12.6 × 10⁹/L (12.6 × 10³/µm³), with 50% polymorphonuclear cells, 23% lymphocytes, 14% monocytes, and 13% eosinophils. His hemoglobin was 10.4 g/dL, and hematocrit, 30.2%. The platelet count was 280 × 10⁹/L (280 × 10³/µm³), and the ESR was elevated at 48 mm/h. The anti‐streptolysin O titer was 170 IU/mL (upper limit of normal, 100 IU/mL [not Todd units]). Urinalysis findings were normal. Blood culture was repeated (4 days after the only vancomycin dose) and was negative. Two-dimensional echocardiography showed a minimal pericardial effusion with no coronary vascular abnormalities.

The patient was treated with nafcillin intravenously from the eighth to the tenth day of illness, at which time results of another blood culture were negative in 48 hours. On the tenth day of illness KS was diagnosed on the basis of the persistence of fever and occurrence of four of five diagnostic criteria, accompanied by desquamation. He was treated for KS with intravenous immunoglobulin (2 g/kg) and high-dose aspirin. The next day the patient became afebrile and remained afebrile thereafter. The platelet count reached a high of 459 × 10⁹/L (459 × 10³/µm³), and the ESR, a high of 59 mm/h on the twelfth day of illness. On day 14 of illness the patient was discharged to home. Findings of follow-up evaluations, including echocardiography, have been normal.
Methods

The *S. aureus* strains from patient 1, designated TXDE, and from patient 2, designated MNTW, were cultured over night on Todd-Hewitt 1% agar (Difco Laboratories, Detroit) in 7% CO₂ at 37°C. Hyperimmune rabbit antisera (20 μL/well) specific for each toxin were added to 4-mm wells punched 4 mm from the growing organism. Control purified toxins (20 μL/well at 50 μg/mL) were added to wells punched 4 mm from the wells containing antisera. The plate was then returned to the CO₂ incubator for 6 hours and was examined for the presence of a precipitin line forming an identity reaction with the adjacent control toxin [4]. The strains were positive for staphylococcal enterotoxin B and negative for TSST-1, enterotoxin C, and exfoliative toxins A and B (figure 1).

Discussion

The diagnosis of KS is particularly difficult in infants, such as patient 1, because often the signs and symptoms are subtle and not all of the diagnostic criteria are met. These children with incomplete clinical features of KS, often termed “atypical KS,” are at increased risk for the development of coronary artery aneurysms [5]. The staphylococcal osteomyelitis in patient 1 was confirmed by physical examination, ⁹⁹Tc bone scan, MRI, and a blood culture that was positive for *S. aureus*. This patient had fever for 13 days despite appropriate antibiotic therapy for osteomyelitis and had three of the five diagnostic criteria for KS.

In addition, this infant had extreme irritability that is characteristic of KS in infants and developed profound thrombocytosis (1,800 × 10⁹ cells/L [1,800 × 10⁹ cells/mm³]) at 15 days of illness, accompanied by the onset of periungual desquamation. He also developed a sterile joint effusion of the right knee late in the course of his illness (day 10), not associated with a focus of osteomyelitis documented by MRI or plain radiography. The osteomyelitis and manifestations of KS in this child appeared clinically to develop concomitantly and not sequentially.

The differential diagnosis for patient 2 included streptococcal pharyngitis with possible scarlet fever, drug reaction, and *S. aureus* bacteremia with toxin-mediated disease that may have been aborted or ameliorated by the dose of vancomycin administered on day 4 of the illness. He had four of five diagnostic criteria for KS, with thrombocytosis (to 459 × 10⁹ cells/L [459 × 10⁹ cells/mm³]) that peaked on the twelfth day of illness. Similar to patient 1, he also developed focal arthralgia (of the right knee) late in the course of his illness (day 8). Although a throat culture was not performed, there was laboratory evidence (a positive rapid antigen test and a modestly elevated antistreptolysin O antibody titer) of group A streptococcal infection in addition to the positive blood culture for *S. aureus*. It is possible that simultaneous staphylococcal and streptococcal infections contributed to his symptoms.

There is evidence supporting a role for superantigens in the pathogenesis of KS. Immunologic alterations in acute KS include T cell activation with production of multiple cytokines by T cells and monocytes [2], as would be expected in a superantigen-mediated illness. The report by Leung et al. of TSST-1-secreting *S. aureus* isolated from 11 of 16 patients with KS initially focused interest on TSST-1 as a potential cause of KS [3]. TSST-1 causes expansion of Vβ2+ T cells, and Abe et al. reported expansion of T cells expressing Vβ2 and Vβ8 in eight of 14 patients with KS [6]. The occurrence of KS with coronary artery aneurysms in several patients with staphylococcal toxic shock syndrome has been reported [7]. Curtis et al. reported colonization with toxin-secreting *S. aureus* in six of 20 patients with KS [8]. Two of the six positive strains secreted TSST-1; staphylococcal enterotoxins A, B, C and D were each secreted by one strain.

Transient decreased T-cell proliferation in response to stimulation with streptococcal pyrogenic exotoxin C was recently demonstrated in children with acute and early convalescent KS, suggesting that this was caused by either superantigen-induced anergy or movement of superantigen-responding cells to sites of inflammation [9].

Investigators of the association of KS with TSST-1 and other bacterial exotoxins have reported inconsistent findings. Choi et al. reported clonal expansion of T cells in KS, consistent with stimulation by a conventional antigen rather than a superantigen [10]. Sakaguchi et al. did not find expansion of Vβ2+ T cells in patients with KS [11], and other groups have also been unable to demonstrate evidence of superantigen-mediated T cell expansion in KS. Because Vβ expansion is transient in superantigen-mediated illnesses, the timing of sampling of T cells from patients may affect the ability to detect this phenomenon. Terai et al. also did not find evidence of superantigen production in supernatants of bacterial isolates from the skin.

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**Figure 1.** Characterization of enterotoxin B secretion from the *Staphylococcus aureus* strain (TXDE) from patient 1. A precipitin line formed between hyperimmune antibodies to staphylococcal enterotoxin B (Anti SEB) and both this *S. aureus* strain and control SEB.
and throat of patients with KS, and they did not find an increased rate of seroconversion to TSST-1 and staphylococcal enterotoxins A, B, and C in patients with KS [12].

A significant problem of studies supporting the involvement of bacterial superantigens in the pathogenesis of KS is the reliance on cultures of skin and mucous membranes. Although Leung et al. showed a higher rate of staphylococcal colonization in children with KS than in controls, it is difficult to establish a causal role for these commensal organisms in the patients’ illnesses. Likewise, the organisms studied by Terai et al. and found to have a low incidence of mitogenic activity were colonizing the patients, and their lack of superantigen activity does not exclude the possibility of other, toxin-producing organisms producing the illness in these patients.

For this reason, the report of KS-like illness associated with infection with toxin-producing S. aureus adds provocative data to the debate of the pathogenesis of KS. These two cases suggest that staphylococcal enterotoxin B may play a role in the pathogenesis of at least some cases of the entity clinically defined as KS. These particular S. aureus isolates may be useful in elucidating the mechanisms responsible for KS-like illness resulting from staphylococcal infections.

The clinical manifestations of KS may be a final common pathway resulting from immune activation from a variety of causes, including bacterial superantigens in some cases. The current diagnostic criteria for KS exclude patients with documented staphylococcal or streptococcal infections. It remains important to exclude the presence of bacterial infections in patients who otherwise meet the diagnostic criteria for KS.

The overlap of clinical symptoms of KS and toxin-mediated streptococcal and staphylococcal infections can make it difficult to distinguish them clinically [13, 14]. However, cases of group A streptococcal infection as well as staphylococcal toxic shock syndrome associated with KS and coronary artery abnormalities have been reported [15, 16]. Those cases, and these two cases of S. aureus infection complicated by symptoms of KS-like illness, suggest the possible role of staphylococcal and streptococcal toxins in some cases of KS. The possibility of a KS-like illness should be considered for children with staphylococcal and streptococcal infections who otherwise fulfill the diagnostic criteria for KS, especially those who have a prolonged febrile course despite appropriate antibiotic therapy.

References