


Kawasaki syndrome: role of superantigens revisited

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Keywords

coronary artery; Kawasaki syndrome; vasculitis

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(Received 7 May 2020, revised 18 June 2020, accepted 5 August 2020)

doi:10.1111/febs.15512

Kawasaki syndrome (KS) is an acute vasculitis in children complicated by the development of heart disease. Despite its description over 50 years ago, the etiology of coronary artery disease in KS is unknown. High dose intravenous immunoglobulin is the most effective approach to reduce cardiovascular complications. It remains unclear why patients with KS develop coronary artery aneurysms. A subset of patients is resistant to immunoglobulin therapy. Given the heterogeneity of clinical features, variability of history, and therapeutic response, KS may be a cluster of phenotypes triggered by multiple infectious agents and influenced by various environmental, genetic, and immunologic responses. The cause of KS is unknown, and a diagnostic test remains lacking. A better understanding of mechanisms leading to acute KS would contribute to a more precision medicine approach for this complex disease. In the current viewpoint, we make the case for microbial superantigens as important causes of KS.

Introduction

Kawasaki syndrome (KS) is an acute multisystem vasculitis associated with immune activation and vascular endothelial dysfunction [1,2]. It is the leading cause of acquired heart disease in children throughout the world, with a particularly high prevalence in Asia. Despite its discovery over 50 years ago, the KS etiology and the pathogenesis of coronary artery aneurysms are unknown, but many potential causes and risk factors have been identified [3]. The combination of aspirin and high dose intravenous immunoglobulin (IVIG) is highly effective in reducing cardiovascular complications [4]. It remains unclear why only 25% of patients with KS develop coronary artery aneurysms and why a small subset of patients develop coronary artery disease despite IVIG treatment [5,6].

Given the heterogeneity of clinical features, variability of natural history, and therapeutic response, it is more accurate to refer to KS as a syndrome, capturing the likelihood we are dealing with a cluster of

phenotypes triggered by multiple infectious agents and influenced by various environmental, genetic, and immunologic responses. A better understanding of mechanisms leading to acute KS would likely contribute to a more precision medicine approach for this complex syndrome. In the current review, we make the case for microbial superantigens as significant causes of KS.

Clinical features of KS

The diagnosis of acute KS is based on clinical criteria defined by the American Heart Association [1]. This includes the presence of fever, bilateral nonexudative conjunctival injection, inflammation of the oropharyngeal mucosa, erythema of the palms or soles during acute KS or periungual desquamation during convalescent KS, and cervical lymphadenopathy. In atypical cases, patients with fever and fewer principal

Abbreviations

IVIG, intravenous immunoglobulin; KS, Kawasaki syndrome; SEs, staphylococcal enterotoxins; SPEs, streptococcal pyrogenic exotoxins; TSST-1, staphylococcal TSS toxin-1; V β -TCR, variable part of the β -chain of the T lymphocyte receptor.

symptoms can be called KS when coronary artery disease is detected.

Kawasaki syndrome has a variety of clinical features which overlap with various infectious diseases. The differential diagnosis includes staphylococcal or streptococcal scarlet fever or toxic shock syndrome (TSS), staphylococcal scalded skin syndrome, and juvenile rheumatoid arthritis [7]. Since KS is based on clinical criteria that overlap with other illnesses, diagnostic uncertainties can arise [8].

Cardiovascular manifestations

Cardiovascular findings are characteristic of KS [9–11]. Coronary artery aneurysms occur in approximately 25% of untreated patients. A subset of patients also suffers from aortic or mitral regurgitation due to myocardial involvement.

Laboratory findings in KS

During acute KS, patients develop neutrophilia [12]. Neutrophil activation has been linked to coronary artery involvement in KS [13]. Thrombocytosis is common [14]. Early in KS, C-reactive protein and erythrocyte sedimentation rate are increased [15].

Vascular endothelial damage is observed early in the development of coronary artery disease [16–18]. Acute KS is characterized by activation of lymphocytes and monocyte/macrophages activation [19–21]. There are also increased levels of IL-1, TNF- α , and IL-6, and these cytokines correlate with development of coronary artery disease and IVIG nonresponsiveness [15,22,23]. Gene association studies have implicated polymorphisms in IL-1, TNF- α , IL-6, HLA, and Toll-like receptors indicative of immune responses in KS [24–28]. Finally, treatment of patients with IVIG and aspirin reduces the immune activation associated with this syndrome [29,30]. Importantly, IVIG contains high titers of neutralizing antibodies to microbial superantigens which we have implicated in acute KS. Successful management of patients who are IVIG-resistant with immunosuppressive agents such as corticosteroids, cyclosporin, infliximab, and IL-1 antagonists reinforces the concept that KS is immune-mediated [31–35].

Identification of the etiologic agent(s) triggering KS is key to developing a specific diagnostic test and more effective approaches for the prevention and treatment of KS. Nevertheless, many physicians believe that KS is caused by an infectious agent. Furthermore, the clinical findings in acute KS significantly overlap with bacterial toxin-mediated diseases such as TSS.

The immune activation found in acute KS is characteristic of diseases caused by bacterial superantigens [36]. Staphylococcal TSS toxin-1 (TSST-1) and streptococcal pyrogenic exotoxins (Spe) are well-known superantigens that cause massive stimulation of T cells. Characteristic of superantigens, these bacterial toxins bind directly to amino acid residues outside of the peptide binding groove and selectively stimulate T cells expressing T-cell antigen receptor (TCR) β -chain variable gene segments (V β -TCRs). In contrast, nominal peptide antigens only stimulate a small proportion of T cells.

To determine whether acute KS is caused by superantigen(s), their T cells have been analyzed for V β -TCR expression [37]. Acute KS was associated with V β 2 T-cell expansion. In contrast, cells from control subjects showed no expansion of V β -TCRs. During the convalescence phase of KS, percentages of V β 2-positive returned to normal. This expansion of V β 2-positive T cells is similar to the changes observed in TSS [36]. Since this report, there have been other reports of V β 2 expansion in KS [38–41]. Interestingly, Yamashiro *et al.* [42] have also observed increased V β 2 T cells in the small intestines of children with acute KS. Abe *et al.* [43] have also analyzed the sequences of V β 2 gene segments from patients with acute KS. None of the acute KS V β 2-positive T-cell clones had evidence of clonotypic expansion which is consistent with superantigen stimulation.

T. Kawasaki provided in coded fashion 10 acute and 10 convalescent sera from KS patients to P. M. Schlievert. These were from KS children and thus could not be called adult KS or TSS. When the code was broken for the serum samples, 0/10 acute sera and 5/10 convalescent sera had protective antibodies to TSST-1 ($P < 0.03$). One acute serum was borderline positive and became negative upon convalescence. The data also examined the response simultaneously to three superantigens where no clear pattern was observed [44]. The data indicated that at least five of the children were exposed to TSST-1 during the acute KS phase. It has been shown that infants of 2–3 months age lack antibodies to TSST-1 [45]. Parsonnet *et al.* [46,47] showed that 20% of human populations, including those of Asian descent where KS appears more common, cannot develop protective antibodies. It is thus possible that the lack of development of antibodies from acute KS to convalescence in half the subjects tested resulted in part from the inability of humans to make antibody responses to TSST-1. It has also been shown, like menstrual TSS [48], recurrences of KS occur, although less commonly (approximately 40% for menstrual TSS, compared to 2% for KS) [49].

Leung *et al.* later [50] analyzed patients with acute KS and compared them to control subjects. Superantigen-producing bacteria were found in the majority of patients with acute KS but rarely in the controls ($P < 0001$). Of 13 superantigen-positive cultures from patients with KS, 11 were TSST-1-secreting *Staphylococcus aureus*, and 2 were Group A streptococci producing SpeB and SpeC. Interestingly, TSST-1 and SpeC are known to stimulate V β 2 T cells. Of note, 12 of the 13 culture-positive patients had superantigen-producing *S. aureus* isolated from the pharyngeal or rectal cultures consistent with the concept infection in KS patients begins in the gastrointestinal tract.

A follow-up, double-blinded, six medical center, case-control study was performed [51]. There were 45 acute KS children and 37 febrile matched controls in the study. Cultures from throat, nares, axilla, and perirectal areas were obtained and evaluated independently by both the home medical center diagnostic laboratories and the Schlievert laboratory. When all major staphylococcal and streptococcal superantigens were compared as a group, there was no significant difference observed in superantigen presence between KS cases and febrile controls ($P = 0.078$). However, focusing on those superantigens that skew V β 2-TCRs, there was a significant association of TSST-1 and SpeC with KS compared to the febrile controls ($P = 0.019$). These data support the role of *S. aureus* producing TSST-1 and Group A streptococci producing SpeC in KS.

An additional potentially important finding in the above study was that the Schlievert laboratory was able to isolate TSST-1 producing *S. aureus* and Group A streptococci producing SpeC, whereas the home medical center diagnostic laboratories in general did not find either microbe [51]. The possible difference between the laboratories included the longer time the Schlievert laboratory retained the cultures, allowing TSST-1 and SpeC superantigen-producing bacteria, to grow on blood agar. Many of these strains were inhibited on blood agar for 4–5 days by normal microbiome organisms from mucosal surfaces, and some were slow-growing, though not small colony variants.

As discussed above, acute KS and TSS overlap in many features, including fever, erythematous rash, and peripheral edema. Indeed, TSS was originally called adult KS [52,53]. However, most investigators suggest there are two major criteria that distinguish KS from TSS: (a) KS has associated aneurysm development but not TSS, and (b) conversely, KS lacks hypotension which typifies TSS. These differences are now being blurred. For example, probable TSS is defined by the CDC as TSS with one major criterion absent [54–56]. Cases that fit the criteria of probable TSS without

hypotension have been described as far back as the early 20th century [57]. Some investigators, including Todd *et al.* [58], who named TSS, have described cases of KS superimposed on TSS [59]. Additionally, there have been multiple reports of a KS-shock syndrome [60,61].

Besides the above formal studies, P. M. Schlievert received 27 *S. aureus* isolates from KS children. All of these isolates, as submitted in blinded fashion, produced TSST-1.

COVID-19 and KS/TSS

Once the number of cases of COVID-19 was apparently high enough, a rare KS/TSS-like syndrome was described. This syndrome, also known as multisystem inflammatory syndrome or pediatric inflammatory multisystem syndrome, was well-studied by Whittaker *et al.* [62]. In the study, 58 children were assessed for the new syndrome with comparisons to KS and TSS. It was noted that 78% of cases had evidence of COVID-19 infection prior to development of the new syndrome. All children had fever and variable non-specific symptoms, including vomiting, diarrhea, and abdominal pain. They all showed marked inflammation. Of the 58 cases, 52% had a rash, 45% showed conjunctival injection, and 50% developed shock. Thirteen met the American Heart Association definition of KS. The average age of the children was approximately 9, which is older than children with typical KS. The onset of the new syndrome was 4–5 weeks after the peak occurrence of COVID-19. There are large numbers of studies ongoing to examine this new syndrome, but its direct cause remains unclear. This new syndrome, KS, and TSS have all been described as ‘cytokine storm’ syndromes, with massive overproduction of cytokines [36,63].

Conclusions and future directions

There has been an enormous amount of effort expended to find the cause of KS, and thus far, the cause remains unknown. However, because of many similarities between KS and TSS, we hypothesize that TSST-1 *S. aureus* may be a significant cause. Like in KS, TSS as caused by TSST-1 is a vasculitis with a massive cytokine response. This cytokine response, sometimes called a ‘cytokine storm’, likely explains the majority of features of both syndromes. IVIG, as used to manage patients with KS, and occasionally TSS, has protective antibodies against TSST-1 and other staphylococcal and streptococcal superantigens. Very recent studies of the COVID-19 KS/TSS-like syndrome is also

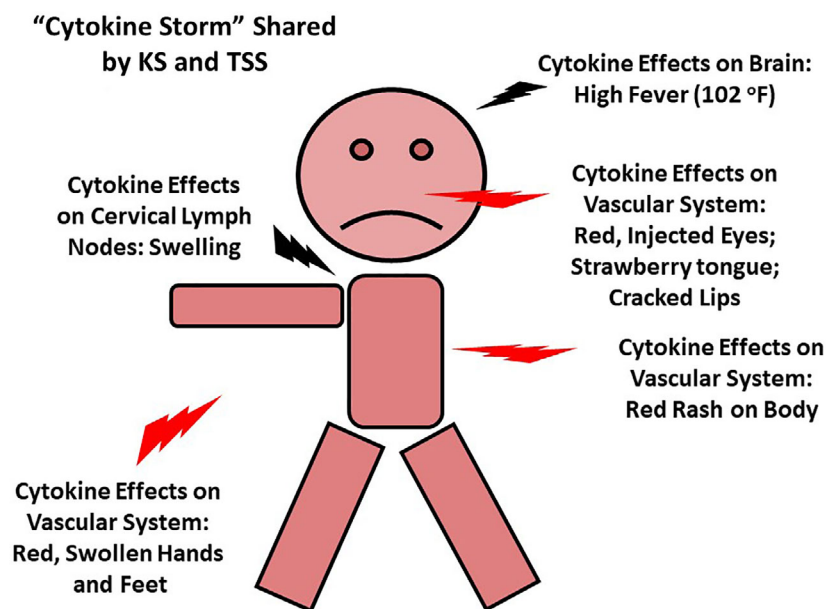


Fig. 1. Kawasaki syndrome (KS) and toxic shock syndrome (TSS) are ‘cytokine storms’ that result in overlapping clinical features due to vasculitis associated with massive cytokine production. Massive cytokine production results in high fever, red skin rash and reddened mucous membranes, cervical lymph node swelling, and edema of the hands and feet.

considered a ‘cytokine storm’ and could be induced either by the SARS-CoV-2 virus alone or by secondary infections, such as by TSST-1 *S. aureus*. Figure 1 summarizes the clinical features of KS and TSS.

It is clear from our discussion that the features of KS and staphylococcal TSS, induced by TSST-1, overlap in many respects. These are listed in Table 1. Some clinicians focus on the rash, with some thinking there is a difference, but others unable to tell the difference. It is a consensus that TSST-1-induced TSS has hypotension as a defining criterion, though this may not be observed in milder cases. The hypotension of TSS results from a vascular capillary leak syndrome caused principally by cytokines, especially TNF. Both KS and TSS are vasculitis diseases. Recently, the new syndrome related to KS and TSS has been described in detail; its association with COVID-19 infection is well-documented but occurs 4–5 weeks post-COVID-19 [62]. The best therapy for this new syndrome could be determined once the precise cause is established. Use of IVIG would neutralize the possible known superantigens, including staphylococcal enterotoxin B, which appears structurally related to SARS-CoV-2 spike proteins.

There are at least three types of experiments that need to be done that may resolve whether or not superantigens are the principal causes of KS. It is already established that superantigens cause TSS [36]. Investigators argue that KS occurs without the need of antibiotic therapy. Lack of responsiveness to antibiotic at one time was stated as a major finding in KS. TSS patients do respond to antibiotics, but there is a high recurrence rate, suggesting incomplete antibiotic

Table 1. Major similarity and differences between KS and TSST-1-induced TSS.

Characteristic	KS	TSS
Fever	+	+
Conjunctival injection	+	+
Mucous membrane changes	+	+
Erythematous rash	+	+
Peripheral edema	+	+
Cervical lymphadenopathy	+	+
Vasculitis	+	+
Vβ2 skewing	+	+
TSST-1 <i>Staphylococcus aureus</i> or SpeC group A streptococci	Significant +; not 100%	+
Hypotension	– ^a	+
Coronary artery aneurysms	May be present	–
‘Cytokine storm’ disease	+	+
Age	< 4 years	All ages
Recurrences	2%	At least 40%

^aHypotension is present in KS-Shock syndrome.

clearance of the causative *S. aureus* [48]. Investigators have argued that they do not isolate *S. aureus* or Group A streptococci from KS cases. The multicenter, double-blinded type of study performed by Leung *et al.* [51] should be repeated by other investigators, retaining and examining all bacteria culture plates for seven days. This should be done for both KS patients and matched, febrile controls.

Second, it will help in clarifying KS causation if TSST-1 producing *S. aureus* can be used to produce

aneurysms and other KS changes in an animal model, for example the rabbit, administered TSST-1 in subcutaneous miniosmotic pumps [64,65]. These pumps are designed to release a certain amount of TSST-1 for 7–28 days. It may be that mice could be used as an alternative. Both models merit consideration.

Recently, there have been news media reports of COVID-19 infection in children who appear to have KS or TSS symptoms. These cases are now commonly referred to as pediatric inflammatory multisystem syndrome. Third, it is important to examine these children for TSST-1 producing *S. aureus* and assessment of V β -TCR skewing. We have previously described postinfluenza TSS in children [66]. A manuscript is posted on bioRxiv at <https://doi.org/10.1101/2020.05.21.109272> by Cheng *et al.*, suggesting the COVID-19 virus, SARS-CoV-2, has spike proteins that are similar to the known superantigen, SEB, associated with non-menstrual TSS [36].

Acknowledgements

The authors acknowledge Nicole Meiklejohn for her assistance in preparing this manuscript. This work was supported by The 5R01 HL37260 grant from NHLBI and a generous gift by The Ann and Louis Rudolph Kawasaki Disease Research Fund at National Jewish Health.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

DYML and PMS conceived and wrote the manuscript and prepared the table and figure.

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