Association of Kawasaki disease with *Staphylococcus aureus* infection

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ABSTRACT

Kawasaki disease (KD) is a common medium vessel vasculitis in children of unknown etiology and is the most common cause of pediatric acquired heart disease. Diagnosis of KD is based on a set of clinical criteria, none of which is individually pathognomonic for this condition. Infections are being considered as one of the predisposing factors. Here, we present three cases, where *Staphylococcus aureus* bloodstream infection was found as the inciting trigger for Kawasaki disease.

Key words: *Mucocutaneous lymph node syndrome, Superantigen, Toxins*

Kawasaki disease (KD) is the leading cause of acquired heart disease in children. The etiology of KD is controversial, and infections are considered to be one of the predisposing factors [1]. Association of KD with superantigen-secreting bacterial infections has come in light through many case reports. In clinical trials done to evaluate the association between KD and superantigen-producing bacteria such as *Staphylococcus aureus* (*S.aureus*) and streptococcus. These bacterias were isolated from the pharynx, axilla, rectum and groin [2,3]. There is one case report of a 10-month-old infant where methicillin-resistant *S. aureus* was isolated from blood [4]. Here, we report three cases of KD having bloodstream infection with *S. aureus*.

CASE REPORT

Case 1

A 2.5-year-old female child was admitted to the department with the complaints of fever for 5 days and rashes for 3 days. Fever was continuous in nature, documented up to 104°F, and was associated with chills. The rash was maculopapular and first appeared on the face, followed by involvement of the trunk. On clinical examination, the child was extremely irritable with stable vitals and normal anthropometry. Detailed examination and laboratory profile are given in Tables 1 and 2. Keeping in view the classical clnical picture, the possibility of KD was kept and the child was treated with intravenous immunoglobulin (IVIG) at 2 g/kg followed by high-dose aspirin at 80 mg/kg/day. The fever, however, continued to persist. Refractory KD was considered, but her blood culture grew methicillin-sensitive *Staphylococcus aureus* (MSSA) which responded to treatment with cloxacillin (100 mg/kg/d in three divided doses) and gentamicin (5 mg/kg/d in two divided doses). The child became afebrile in 48 h. Echocardiography done at admission and 2 weeks later was normal. Aspirin was tapered to low dose at 3 mg/kg/d. The child came for follow-up. The coronary echocardiography was done at 6 weeks and was normal, so her aspirin was stopped.

Case 2

A 3-year-old female child was admitted with the complaints of high-grade fever for 4 days and cough and fast breathing for 3 days. On examination, the child was irritable, with a pulse rate of 150/min and respiratory rate of 90/min along with the use of accessory muscles. Chest examination revealed decreased air entry with crepitations on the right side. On abdominal examination, there was splenomegaly, 2 cm below the costal margin. The possibility of sepsis with pneumonia was kept, and the child was started on injection ceftriaxone (100 mg/kg/d in two divided doses), cloxacillin (100 mg/kg/d in three divided doses), and gentamicin (5 mg/kg/d in two divided doses). The child required ventilatory and inotropic support for respiratory failure and shock. With no clinical signs of improvement after 48 h, injection vancomycin was started in place of cloxacillin. Subsequently, the child improved, inotropes were tapered off, and she was successfully extubated after 48 h. She became afebrile after 72 h. However, there was a recurrence of fever on day 7. Considering nosocomial sepsis, she was started on injection piperacillin-tazobactam (200 mg/kg/d in three divided doses). Vancomycin and gentamicin were continued, but fever persisted, and subsequently, she developed features of KD. Detailed examination and laboratory profile of the child are given in Tables 1 and 2. She was given IVIG 2 g/kg on day 12 of admission, along with aspirin at 80 mg/kg/d, to which the fever responded. Initially, her echocardiography was normal, but later on, the repeated investigation revealed aneurysms in the right and

Table 1: Demographic and clinical profile of the patients

Parameter	Case 1	Case 2	Case 3
Age (years)	2.5	3	5
Sex	Female	Female	Female
Fever	Yes×5 days	Yes×4 days	Yes×4 days
Irritability	Extreme	Extreme	Extreme
Focus of infection	No	Pneumonia	Pneumonia with abscess
Rash	Erythematous maculopapular	Not present	Erythematous maculopapular
Cervical lymphadenopathy	Left cervical	Bilateral cervical	Not present
Non-purulent conjunctivitis	Bilateral present	Bilateral present	Not present
Acral edema, periungual, and perianal exfoliation	Present	Present	Present
Cracked lips/strawberry tongue	Present	Present	Present
Shock	No	Yes	No
Echocardiography	Normal study	Normal initially. Repeated at 2 weeks: 5-mm dilatation of the left coronary artery and 3-mm dilatation of the right coronary artery.	3.5-mm dilatation of the left coronary artery and 4.5-mm dilatation of the right coronary artery
Impression	Complete KD	Complete KD	Incomplete KD
Treatment given for KD	IVIG 2 g/kg Aspirin 80 mg/kg/d	IVIG 2 g/kg Aspirin 80 mg/kg/d	IVIG 2 g/kg Aspirin 80 mg/kg/d
Antibiotics given	Intravenous Cloxacillin×10 days Gentamicin×7 days	IV cloxacillin×2 days Ceftriaxone×7 days Gentamicin×10 days, Vancomycin×14 days Piperacillin and tazobactam×7 days	Intravenous Ceftriaxone×7 days, Vancomycin×14 days

IVIG: Intravenous immunoglobulin, KD: Kawasaki disease

Table 2: Laboratory profile of the patients

Parameter	Case 1	Case 2	Case 3
Hemoglobin (g%)	11.2	10.3	8.2
Total leukocyte count	12,000/mm^3	10400/mm^3	15800/mm^3
Differential leukocyte count (%)	N76, L20	N86, L10	N84, L12
Platelets (lakhs/mm^3)	Day 1: 2.10 Day 7: 7.0	Day 1: 3.2 Day 7: 6.0	Day 1: 0.45 Day 14:8.42
C-reactive protein (mg/L)	Positive > 12	Positive > 24	Positive > 12
Erythrocyte sedimentation rate (mm 1st h)	35	25	55
Total serum bilirubin (mg/dl)	0.3	0.2	0.29
Aspartate aminotransferase (IU/L)	30	120	138
Alanine transaminase (IU/L)	34	98	115
Serum albumin (g/dl)	3.5	2.2	2.5
Blood culture	MSSA	MSSA	Sterile

MSSA: Methicillin-sensitive *Staphylococcus aureus*

left coronary arteries. She was under regular follow-up and on long-term aspirin prophylaxis at 3 mg/kg/d.

Case 3

A 5-year-old female child was referred with complaints of boil over the left buttock for 9 days and fever for 4 days. On examination, the child had an abscess over the buttock and was in respiratory distress. She was treated as staphylococcal septicemia with pneumonia and was started on injection ceftriaxone (100 mg/kg/d in two divided doses) and vancomycin (60 mg/kg/d in three divided doses). Her abscess was drained and pus was sent for culture and sensitivity. On day 5 of hospital stay, she developed pain and swelling over the right leg. Ultrasonography revealed deep vein thrombosis, which was treated with low molecular weight heparin followed by warfarin. Blood and pus cultures were sterile, probably due to prior use of antibiotics. She became afebrile after 7 days. On day 12 of hospital stay, she again started having a fever along with the features that were suggestive of incomplete KD. Details are given in Tables 1 and 2. She was treated with IVIG at 2 g/kg and aspirin 80 mg/kg/d. Her ECHO revealed 3.5-mm dilatation of left coronary artery and 4.5-mm dilatation of the right coronary artery.

The child was under regular follow-up and on long-term aspirin prophylaxis.

DISCUSSION

KD was first addressed by Tomisaku Kawasaki as an acute febrile mucocutaneous lymph node syndrome in 1967. This disease has the potential to cause coronary artery aneurysms (CAA) and myocardial infarction later in life. KD is prevalent worldwide, and it affects children of all races. Asians-Pacific regions are believed to be at higher risk. In the late 1990s, the pediatrician in India believed that KD does not exist in our country. Now, the awareness about the disease has increased in India and many physicians are diagnosing and managing the condition. As per experts, children with KD are still being missed in India [1]. The hospital-based registry at Chandigarh showed that the incidence of KD had increased from 0.51 to 4.54/100,000 children aged <15 years during 1994–2007 [2].

KD is diagnosed based on a set of clinical diagnostic criteria. These criteria are fever of at least 5 days' duration and presence of any four of the following five features: Changes in extremities, polymorphous exanthema, bilateral conjunctival injection, changes in the lips and oral cavity, and cervical lymphadenopathy. Children presenting with fever and fewer than four of the other clinical features are said to have "incomplete" KD. Children with incomplete KD have a significant risk of CAA [1].

The etiology of KD is controversial, and infections are considered to be one of the predisposing factors [3]. The etiology and pathogenesis of KD are an important and worthwhile public health concern [4]. Regarding the etiology, several hypotheses, from tropospheric wind patterns by Dr. Burns to the superantigen theory by several authors, have been proposed, but none have been conclusive till date [3-6].

There is one case report of a 10-month-old infant where methicillin-resistant *S. aureus* was isolated from blood [4]. The possibility of an infectious etiology of KD disease stems from the fact that there is a marked seasonality, temporal, geographic, and family clustering of cases, and the highest incidence rates are seen among 6-month–2-year-old children, who are most susceptible to infections [7]. Several studies have proposed that infection with superantigen-producing bacteria such as S. aureus and streptococcus may be the etiopathogenetic mechanism underlying KD [4-6]. Furthermore, there is some similarity in the clinical findings between KD, staphylococcal, and streptococcal toxic shock syndrome [4].

The clinical trials to evaluate the association between superantigen-producing bacteria such as S. aureus, streptococcus,and KD have found superantigen-secreting bacteria from the rectum, pharynx, axilla, and groin [4]. Previously, in all but one study, bacteria were cultured without an obvious focus, from mucocutaneous sites [5,8]. This is an indirect evidence, as it proves colonization and not an infection. Thus, for a more direct evidence, a culture of the organism from blood may be relatively important. In our study, all three cases had a clinical course consistent with staphylococcal sepsis. MSSA was isolated in two cases, while in one case, the cultures were sterile, probably due to prior antibiotic usage.

CONCLUSION

The temporal association between staphylococcal bacteremia and KD can be suggested based on the above-mentioned cases. Therefore, in children with staphylococcal infection, where there is re occurrence or persistence of fever despite adequate antibiotic coverage, one must consider KD.

REFERENCES

1. Singh S, Kawasaki T. KD: An Indian perspective. Indian Pediatr 2009;46:563-71.
2. Singh S, Aulakh R, Bhalla AK, Suri D, Manojkumar R, Narula N, *et al*. Is kawasaki disease incidence rising in Chandigarh, North India? Arch Dis Child 2011;96:137-40.
3. Singh S, Sharma D, Bhattad S, Phillip S. Recent advances in kawasaki disease–proceedings of the 3rd Kawasaki disease summit, Chandigarh, 2014. Indian J Pediatr 2016;83:47-52.
4. Pan HS, Chen FL, Sun HL. Methicillin-resistant *Staphylococcus aureus* bacteremia complicated with a typical Kawasaki disease. Austin J Allergy 2014;1:3.
5. Leung DY, Meissner HC, Fulton DR, Murray DL, Kotzin BL, Schlievert PM, *et al*. Toxic shock syndrome toxin-secreting *Staphylococcus aureus* in Kawasaki syndrome. Lancet 1993;342:1385-8.
6. Leung DY, Sullivan KE, Brown-Whitehorn TF, Fehringer AP, Allen P, Finkel TH, *et al*. Association of toxic shock syndrome toxin-secreting and exfoliative toxin-secreting *Staphylococcus aureus* with Kawasaki disease complicated by coronary artery disease. Pediatr Res 1997;42:268-72.
7. Chang LY, Lu CY, Shao PL, Lee PI, Lin MT, Fan TY, *et al*. Viral infections associated with Kawasaki disease. J Formos Med Assoc 2014;113:148-54.
8. Yoshioka T, Matsutani T, Iwagami S, Toyosaki-Maeda T, Yutsudo T, Tsuruta Y, *et al*. Polyclonal expansion of TCRBV2- and TCRBV6-bearing T cells in patients with Kawasaki disease. Immunology 1999;96:465-72.

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