

Skin rash and cervical lymphadenopathy in a febrile male baby

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A 10-month old male baby was brought to the dermatology out-patient department with complaints of high grade fever, polymorphic skin rash, and swelling of hands and feet of 5 days' duration. There was no history suggestive of any focus of infection such as sore throat, cough, diarrhea, ear discharge, etc. There was no family history of similar complaints. The child was not on any medication at the time of appearance of his signs and symptoms.

The general physical examination revealed a febrile child with bilateral cervical lymphadenopathy and intense redness of conjunctivae and oral mucosa.

His cutaneous examination revealed generalized erythematous maculopapular rash on the face, trunk and limbs (Fig. 1 & 2). There were a few purpuric lesions on the legs. In addition, he had edema over his hands and feet, and dryness, erosions and haemorrhagic crusting on the lips (Fig. 3). His genital mucosa, palms, soles, nails and scalp were normal.



Fig. 1 Maculopapular rash on trunk.



Fig. 2 Maculopapular rash on lower limbs with edema of feet.



Fig. 3 Rash on face with dry, fissured lips and haemorrhagic crusts.

His investigations revealed leukocytosis (WBC 14000 /ml), raised ESR (41 mm/ first hour), and CRP (34 mg/l). The, LFT, RFT, urinalysis, ASOT were normal. Throat, urine, stool, and blood cultures were negative. His chest x-ray, ECG and echocardiography were normal.

What is your clinical differential diagnosis?

1. Kawasaki's disease
2. Viral exanthema
3. Fifth disease

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The child was given a single high dose (2g/kg) of intravenous immunoglobulin (IVIG) with excellent response in his signs and symptoms. Fever subsided within 2-days. The skin rash started desquamating within 2-days of giving IVIG (Fig.4) and cleared completely after 2-weeks. Edema of hands and feet cleared in a week's duration (Fig. 5). His conjunctival redness disappeared within one day, whereas fissuring and crusting over lips cleared in 3-days' time. His laboratory parameters started improving from the day after the IVIG and became normal within 5-days.



Fig. 4 Rash on forearm and swelling of hand subsiding with exfoliation after few days.



Fig. 5 Marked reduction of swelling of feet and rash after IVIG.

DISCUSSION

Kawasaki disease (KD) also known as acute febrile mucocutaneous lymph node syndrome was first described by Tomisoku Kawasaki in 50 children from Japan in 1967.¹ KD is the most common cause of multisystem vasculitis in childhood, making KD the number one cause of acquired heart disease in children in the developed world because the vessels most commonly affected are

the coronary arteries.² Although initially thought to be rare and occurs most commonly in Japan, Approximately 10000 new cases are diagnosed every year in Japan and more than 3000 in US. KD has now been reported from many countries around the world.

The exact etiology is unknown but infections or superantigens related to pathogenic organisms have been hypothesized to trigger the condition. Viruses, conventional as well as superantigens related to bacteria, and genetic polymorphisms have been implicated in the etiology of the disease. Markers of inflammation, such as CCL2 and CCXCL10, contribute to the pathology and the diagnosis of KD.³

Genetic predisposition is clearly implicated as demonstrated by genetic analysis of affected Japanese children revealing ITPKC, 1,4,5-triphosphate 3-kinase C, a kinase involved in regulation of T-cell activation, to be significantly associated with susceptibility to and increased severity of KD.⁴ Regulation of T-cell activation has emerged as the critical factor in determining susceptibility and severity of KD.²

Two previously proposed theories of etiology of KD, the toxic shock syndrome toxin-1 hypothesis and the coronavirus NL-63 hypothesis, have been studied extensively and disproven.⁵

Histologically, coronary arteritis begins 6-8 days after the onset of KD, and leads immediately to inflammation of all layers of the artery. The inflammation spreads completely around the artery; causing extensive damage to the structural components of the artery. The artery then begins to dilate. Inflammatory cell infiltration continues until about the 25th day of the disease, after which the inflammatory cells gradually decrease in number but fibrosis can occur. KD arteritis is character-

ized by granulomatous inflammation that consists of severe accumulation of monocytes/macrophages. Aberrant activation of monocytes/macrophages is thought to be involved in the formation of vascular lesions. The lesions in all the arteries are relatively synchronous as they evolve from acute to chronic injury. There is no fibrinoid necrosis nor any mixture of acute inflammatory lesions and scarring lesions, which are characteristics in polyarteritis nodosa in KD.⁶

Clinically, KD has 2 stages; acute inflammatory and a chronic stage from damage to the arteries, primarily coronary. KD most frequently affects infants and young children under 5 years of age. Onset is acute with high fever and intense redness of conjunctivae, oral mucosa especially and tongue that can have prominent papillae (strawberry tongue) and dry fissured lips. A generalized maculopapular rash appears after 3-4 days that localizes to hands and feet after 3-4 days. Characteristic edema of hands and feet appears next. Bilateral cervical lymphadenitis is noted in 50% patients. The fever lasts 5-7 days, the rash for few more days. There is accompanying myocarditis in 25% of patients and myocardial infarction in 1-2% cases. Myocarditis manifests as arrhythmia or tachycardia, valvular incompetence and pericarditis may also occur. Coronary artery disease occur secondary to dilatation causing aneurysm that may thrombose. These also resolve after few years in most patients. Rare complications include arthralgia, arthritis, severe erythema multiforme, iritis, hepatitis, and aseptic meningitis.⁷

However certain clinical criteria have been described that are helpful in making a diagnosis of Kawasaki disease. These include high grade fever >5 days, and any 4 of the following 5: edema and redness of hands and feet, oral changes (strawberry

tongue and dry fissured lips), generalized maculopapular rash, non-exudative conjunctivitis, and cervical lymphadenitis (usually unilateral).⁸

KD is an acute, inflammatory, self-limited vasculitis of childhood that can have serious consequences. Progress in treatment during its acute phase has decreased the incidence of coronary artery lesions from 25-30% to 3-5%.⁹

IVIg and aspirin are the main stay of treatment of KD in the acute phase. In the US, the recommended treatment for KD in the acute phase is a single, high dose of intravenous gammaglobulin (2 g/kg) and high dose aspirin (80 to 100 mg/kg/day). Use of this regimen has resulted in a significant decrease in the incidence of coronary artery abnormalities. Although the American Heart Association currently recommends high dose aspirin, moderate doses are used in Japan. Long term pharmacological therapy consists primarily of anticoagulation in patients with persistent coronary artery abnormalities.¹⁰

According to Cochrane survey in 2003, children fulfilling the diagnostic criteria for KD should be treated with IVIG (2 gm/kg single dose) within 10 days of onset of symptoms.¹¹

KD refractory to intravenous administration of immunoglobulin therapy that can happen in 10-15% patients may respond to aspirin, corticosteroids, cyclophosphamide, and/or plasmapheresis.³ Histopathological studies have shown that the changes occurring in vessels in KD are distinct from those of atherosclerosis. However, endothelial dysfunction and risk factors for the development of atherosclerosis, such as dyslipidemia, decreased vascular elasticity, increased C-reactive protein, oxidative stress, inflammatory cytokines, and reactive oxygen species, are known to be present in the late phase of Kawasaki disease.

Therefore long term follow up of children affected by KD into adulthood is required to assess this risk. Children diagnosed to have KD need long term follow up to assess, prevent and manage late sequelae of coronary artery disease when they grow up.¹² Incomplete and atypical forms of KD are frequently reported and one should be aware of these.^{13,14}

CONCLUSION

Although uncommon, incidence of KD is increasing worldwide. Awareness among primary physicians, paediatricians and dermatologists about the condition and its clinical features is of paramount importance to detect this condition early. In absence of confirmatory diagnostic tests, a high index of suspicion and integration of diagnostic criteria to arrive at an early diagnosis can prevent potential serious sequelae as institution of early treatment with IVIG and aspirin is highly effective in achieving this goal. The current investigations may provide the answer to its etiology, suspected to be infectious in nature.

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