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# Kawasaki Disease Associated with Parainfluenza Type 3 Virus Infection

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**Running Head:** Kawasaki Disease

**SUMMARY** Kawasaki disease (KD) is an acute, febrile and multisystem vasculitis of early childhood with a striking predilection for the coronary arteries. In developed countries, the incidence of KD has replaced acute rheumatic fever as the leading cause of acquired heart disease in children. The etiologic agent of KD remains unknown, although clinical and epidemiologic features strongly indicate an infectious cause. Parainfluenza viruses are the major cause of laryngotracheobronchitis (croup), but they also commonly cause upper respiratory tract infection, pneumonia, or bronchiolitis. Types 1 and 2 viruses are the most common pathogens associated with croup, and type 3 viruses are associated with bronchiolitis and pneumonia in infants and young children. Rarely, mumps, aseptic meningitis, and encephalitis have been associated with type 3 infections. We report a patient with typical KD during parainfluenza type 3 infection.

**KEY WORDS** Kawasaki disease, parainfluenza, etiology

## INTRODUCTION

Kawasaki disease (KD) is an acute systemic vasculitis of childhood. Children predominantly affected are less than 5 years of age, and coronary artery involvement is responsible for most of the disease morbidity and mortality (1,2). Whereas many infective agents including viruses have been postulated as the possible causes of KD, no single agent has been shown definitely to be associated with this disease and the causative agent remains elusive (2,3). This report describes a patient with the diagnostic criteria of typical KD during concomitant parainfluenza type 3 infection and we discuss the possible role of this virus in the etiology of KD.

## CASE REPORT

We present a 7-year-old Caucasian boy that recurred to the pediatric emergency with a five-day history of polymorphous rash, edema of the hands and feet, and fever. Clinical examination showed macular and papular exanthema particularly noticeable on the trunk and proximal extremities,

Acta Dermatovenerol Croat
2010;18(2):120-123

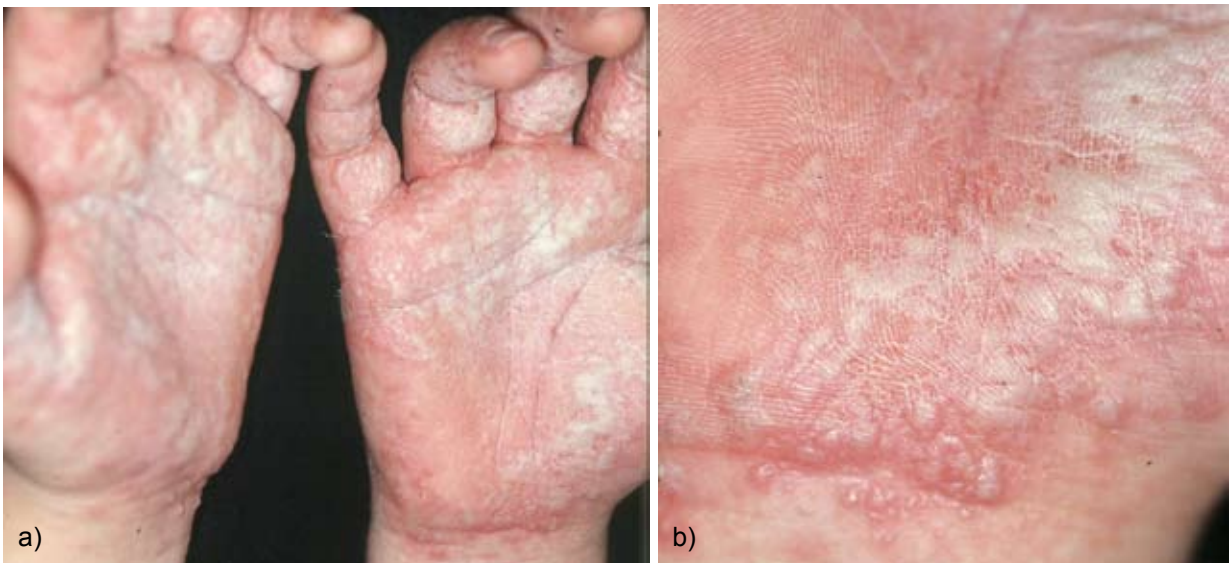


**Figure 1.** (a) Edema and induration of the hands; (b) pustules of the palms.

pustules of the palms and soles, edema with induration of the hands and feet (Fig. 1A, B), perineal erythema (Fig. 2), strawberry tongue, "cherry" red swelling and fissuring of the lips (Fig. 3), and non-exudative conjunctivitis. Fever was as high as 39 ºC with malaise and there was a 15-mm left cervical lymphadenopathy. The remaining physical examination was normal and the child was admitted to the pediatric department.

Laboratory findings revealed an increase in erythrocyte sedimentation rate and C-reactive protein, and leukocytosis with a predominance of neutrophils. The levels of platelets, hemoglobin, serum electrolytes, aspartate and alanine aminotransferase, blood urea nitrogen and serum creatinine were normal. The chest radiograph was also normal. No bacterial or fungal agent was demonstrated on cultures of blood or urine samples.

Serologic tests were negative for influenza A and B viruses, Epstein-Barr virus, cytomegalovirus, parainfluenza type 1, parvovirus B19, adenovirus, measles virus, respiratory syncytial virus, *Mycoplasma pneumoniae*, toxoplasmosis and human herpesviruses types 1 and 2. Serology was IgM-positive for parainfluenza type 3 in a complement-fixing reaction.

Electrocardiography and echocardiographic evaluation were normal.

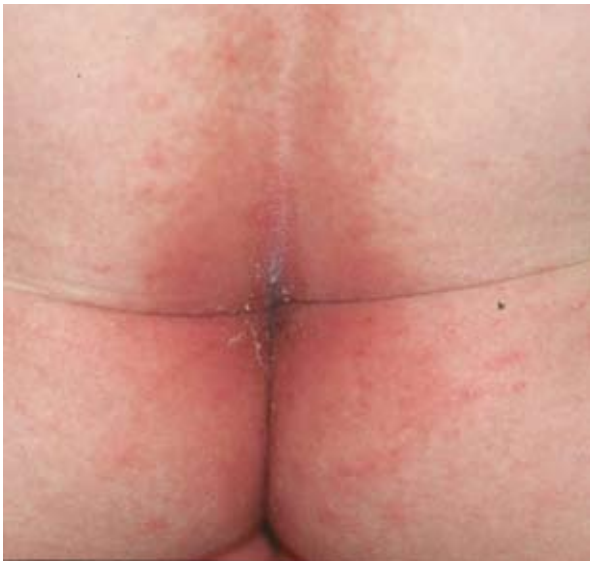

**Figure 2.** Perineal erythema with desquamation.

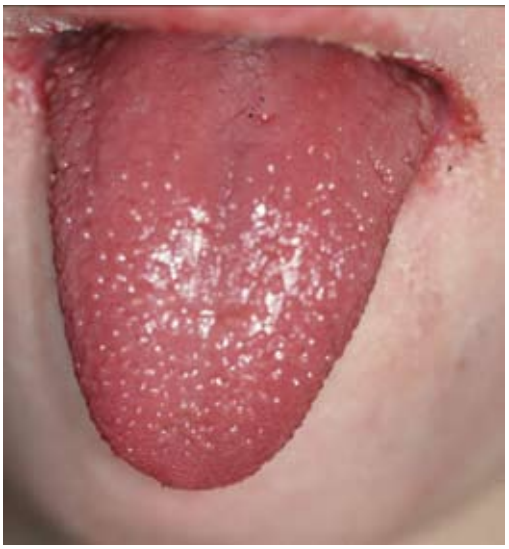

**Figure 3.** Strawberry tongue, "cherry" red, swelling and fissuring of the lips.

Acta Dermatovenerol Croat
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It was decided to start treatment with 2 g/kg of intravenous immunoglobulin as a single infusion and oral aspirin at a dosage of 60 mg/kg/d until the fever subsided.

Apyrexia, improvement of the general state and perineum and periungual desquamation were seen within 48 hours.

He was discharged from the hospital 3 days later without apparent sequels. At 1-year follow up, he showed normal physical, laboratory and echocardiography findings.

## DISCUSSION

There is no specific diagnostic test for KD. Diagnosis is based on clinical criteria that include fever, bilateral conjunctival injection, oropharyngeal and peripheral extremity changes, polymorphous rash and cervical lymphadenopathy. Fever of at least 5-day duration and the presence of at least four of the clinical criteria previously cited are sufficient for the diagnosis (1,3,4). Our patient presented with six clinical criteria for KD.

Despite 40 years of research, the etiology of KD remains unknown and consequently there is no diagnostic test and treatment is nonspecific and suboptimal. The consensus is that KD is due to one or more widely distributed infectious agent(s), which evoke an abnormal immune response in genetically susceptible individuals (2,3,5).

Much of the continuing debate in the literature concerns whether KD is caused by a superantigen or conventional antigen. KD shares many clinical features with superantigen-mediated disease (for example, rash, conjunctivitis and skin peeling) and KD has occasionally been reported concurrently in children with toxic-shock syndrome, which is caused by superantigens. However, unequivocal epidemiological and laboratory support for the role for superantigens in KD is lacking. Superantigens bind to the Vβ region of the T-cell receptor and clonal expansion of Vβ2-expressing T-cells has been reported in some studies of KD, but again these findings are inconsistent. Recent studies suggest that gut bacteria might be involved in KD, producing superantigens and heat shock proteins (6,7).

Other studies have reported oligoclonal IgA-producing plasma cells infiltrating bronchial and intestinal tissues in fatal KD, which suggests the involvement of a conventional antigen (1,3). A recent paper says that the IgM transcripts expressed by the B cells in peripheral blood of KD patients in the acute phase of the disease clearly show an oligoclonal expansion, suggesting that KD is caused not by stimulation of a superantigen, but rather by a conventional antigen (8).

Virus infections and bacterial toxins with superantigenic properties, secreted by certain strains of *Staphylococcus aureus* or group A beta-hemolytic *Streptococcus pyogenes*, have been described as pathogenic mediators. Accumulating data note that viruses have an important role in human vasculitic disease. The epidemiology of KD, with rapid changes in the incidence, seasonal variation and relationship between the incidence and weather conditions, certainly is more suggestive of acute viral infections than bacterial colonization, which alters more slowly (2,5).

Many organisms and toxins have been reported as the possible agents in the disease: *Staphylococcus* species, *Streptococcus* species, *Rickettsia* species, herpesvirus, human coronavirus New Haven, Epstein-Barr virus, parvovirus B19, adenovirus, measles virus, retrovirus, cytomegalovirus, and others. The list of discarded and/or unproven etiological agents in KD is long.

According to the present hypothesis, the etiologic agent for KD is a ubiquitous virus that causes clinical vasculitis in genetically susceptible individuals (2-5).

We emphasize the parainfluenza virus as a common cause of lower and upper respiratory tract infection in children. These patients have higher nasal concentrations of interleukin-6, interleukin-8, macrophage inflammatory protein-1alpha and -1beta and RANTES. This virus infection causes a spectrum of illnesses associated with the expression and release of several proinflammatory mediators (9).

Much of the controversy and inconsistency surrounding the nature of the infectious trigger in KD might reflect multiple etiologic agents resulting in the same clinical phenotype.

The present case emphasizes the possible relationship between parainfluenza type 3 and KD. To our knowledge, this is the third case reported in the English literature (10,11).

We conclude that it is important to report these associations, trying to realize what these triggering agents have in common.

Specific diagnostic test(s) and rational interventions could be readily developed if the etiopathogenesis of KD was fully understood. Moreover, preventive treatments such as vaccines would be justified in populations with the highest KD inci-

Acta Dermatovenerol Croat
2010;18(2):120-123

dence, where KD affects 1%-2% of all children, such as Korea and Japan (2,3).

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Nice hands with Nivea cream; year 1936.
(from the collection of Mr. Zlatko Puntijar)