CASE REPORT

Kawasaki Disease Case Presentation and Review in childhood: the importance of early recognition.

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Abstract
Kawasaki disease is an acute febrile vasculitis of childhood that predominantly affects the coronary arteries. The cause of Kawasaki disease remains unknown although genetic predisposition and an infectious agent are strongly suspected based on clinical and epidemiologic features.

This disease, which affects children younger than five years, is characterised by prolonged fever plus four of the following five diagnostic criteria: polymorphous rash, non-exudative conjunctivitis, oral-mucosal involvement, extremity desquamation and cervical lymphadenopathy.

The diagnosis should be considered in any highly irritable, febrile child with skin manifestations. Full intravenous immunoglobulin and aspirin, the mainstay of treatment, should be initiated immediately. Prompt recognition of this disease is vital in order to reduce cardiovascular complications such as aneurysms and its sequelae.

We report a case of a four year-old male child that was diagnosed, managed and treated at the Corozal Community Hospital, Belize.

Key words
Kawasaki disease, prolonged fever, vasculitis, intravenous immunoglobulin, aspirin, aneurysms.

■ INTRODUCTION

Kawasaki disease (KD), also known as mucocutaneous lymph node syndrome, is an acute, systemic vasculitis of small- and medium-sized arteries that predominantly affects patients from six months to four years of age. It represents the most prominent cause of acquired coronary artery disease in childhood.(1,2)

It was first reported in the Japanese by Kawasaki in 1967. (3) The aetiology of KD may be attributed to the combined effects of infection, exaggerated immune response, and genetic susceptibility. Suspected pathogens and infections have included the following: parvovirus B19, meningococcus, bacterial toxin-mediated superantigens, adenovirus, parainfluenza type 3 virus, rotavirus infection, measles and Epstein-Barr virus to name some. It is postulated that the virus enters via respiratory route, activating both the innate and adaptive immune systems and resulting in B lymphocytes switching to immunoglobulin A (IgA)-production.(4)

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A functional polymorphism of the inositol 1,4,5-triphosphate 3-kinase C (ITPKC) gene on band 19q13.2 has been found to be significantly associated with an increased susceptibility to developing Kawasaki disease. In addition, this polymorphism was associated with an increased risk of coronary artery lesions in both Japanese and U.S. children.(5)

Kawasaki disease is slightly more common in males than in females. The male-to-female ratio ranges from 1.3–1.83:1. Most of the disease pathology is induced by medium arterial vessel vasculitis. Initially, neutrophils are present in great numbers, but the infiltrate rapidly switches to mononuclear cells, T lymphocytes, and immunoglobulin A(IgA)-producing plasma cells. Eosinophils are preferentially accumulated in microvessels. Inflammation involves all three layers of the vessels. In this period of greatest vascular damage is when a concomitant progressive increase in serum platelet count occurs, and it is the point of the illness when the death risk is most significant.(4)

The clinical presentation is shown in Figure 1. Diagnosis is made by the presence of fever for at least five days (onset of fever considered as day one of illness) and at least four

out of the following five diagnostic criteria that often appear sequentially according to the American Heart Association guidelines(6): (i) conjunctival injection, (ii) erythema of oral and/or pharyngeal mucosa —may include strawberry tongue, red pharynx and/or red and cracked lips, (iii) erythema and oedema of hands and feet. In the sub-acute phase of Kawasaki disease (from about day 10 onward), there may be (iv) desquamation of the fingers and toes, (v) polymorphous maculopapular, annular or scarlatiniform skin rash —involvement of the trunk, extremities and face; and (vi) cervical lymphadenopathy— often unilateral and large. The clinical presentation is shown in Figure 1. Incomplete Kawasaki disease refers to infants satisfying fewer than four classic diagnostic criteria.(7)

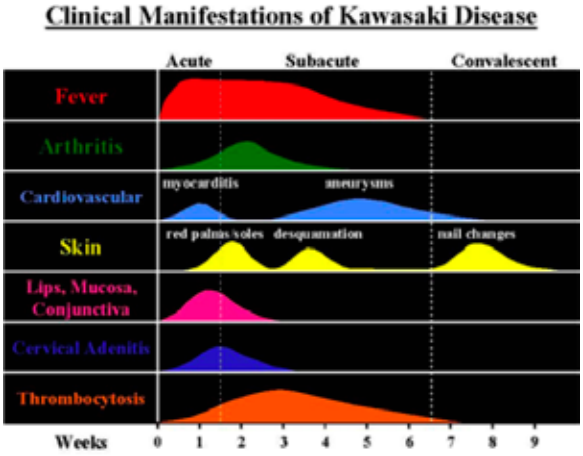

Figure 1 Clinical manifestations and time course of KD (adapted through courtesy of Paul R. Ogershok MD).

There is no specific diagnostic test. However, certain laboratory findings are characteristic, although none have high individual positive predictive value. These include: leucocytosis with neutrophilia, markedly elevated erythrocyte sedimentation rate and C-reactive protein, hypoalbuminaemia, anaemia (normocytic, normochromic), mildly raised liver enzymes (predominantly alanine aminotransferase) and platelet count that increases markedly by the second week of illness.(4,7)

Intravenous immunoglobulin (IVIG) is the only proven therapy that improves coronary artery outcomes, reducing the incidence of coronary artery aneurysms to 2–5% and should preferably be given within 10 days of fever onset, but at any time if the child is febrile or there are laboratory features of persisting inflammation. High dose aspirin is usually given in addition to this treatment, although its use has never been subjected to a randomised controlled trial and the dosing regimen is somewhat controversial.(8,9)

Echocardiography is the study of choice to evaluate for coronary artery aneurysms. Serial echocardiograms should be obtained at the time of diagnosis, at 2 weeks and at 6–8 weeks after the onset of the illness.

Prompt recognition of this illness is imperative to avoid long-run cardiovascular complications such as coronary artery aneurysms and its sequelae.

We describe the case of a four year old male child of creole ethnicity that was diagnosed, treated and followed up at the Corozal Community Hospital, Belize.

Figure 2 Edema and erythema of hand in KD

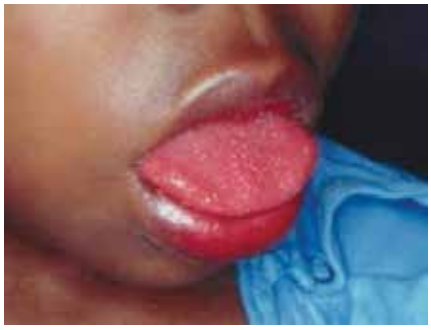

Figure 3 Strawberry tongue in KD

Figure 4 Cracked lips and fissures in KD

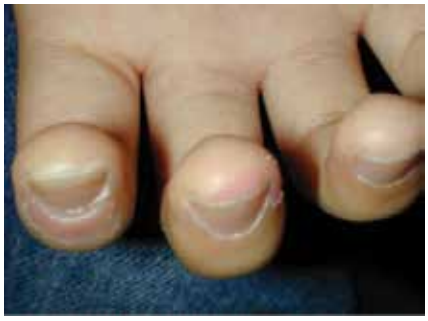

Figure 5 Acral fine desquamation of fingers in KD

■CASE REPORT

A four year old male child, otherwise healthy with unremarkable clinical history is referred with onset one week prior to consultation of left cervical lymphadenitis treated with beta-lactamase antibiotics (cloxacilline, then penicillin), resolving its adenopathy. During this time span, he presented fever for one week, followed by oedema and erythema of hands (Figure 2), wrists and ankles with difficulty to ambulate and loss of hand strength. Accompanying clinical features were strawberry tongue (Figure 3), cracked lips and fissures (Figure 4), pharyngeal oedema/ erythema, conjunctival injection and lethargy.

Immediately a first laboratory workup was conducted with the following results (Table 1): mild anaemia, leucocytosis with neutrophilia, thrombocytosis of 749,000 and elevated erythrosedimentation rate (ESR). Monospot test was reported negative, ruling out infectious mononucleosis or glandular fever. Based on these findings a further clinical evaluation on the second week of illness was conducted encountering at this time fine desquamation of upper back, elbows and finger tips (Figure 5), with fever typically resolving. Kawasaki disease was suggested as the most probable diagnosis based on the five diagnostic criteria,

and due to the accompanying elevation of platelet count to 1,146,000 cells/µl.

Due to the parents' limited financial resources, immediate human IVIG, as the treatment of choice, could not be instituted, but only high dose aspirin at 80mg/kg/day as anti-inflammatory, antiplatelet drug. Fortunately, an echocardiogram, reported no signs of coronary artery aneurysms.

The clinical and laboratory follow-ups of this patient were unremarkable, with fast recovery of platelet count and acute phase reactants (ESR) from the first week through the sixth week of illness as depicted on table 1, and a second echocardiogram performed by then was reported normal.

Tabla 1: Laboratory results at different times

	1st lab. work up	6th day lab. follow-up	9th day lab. follow-up	37th day lab. follow-up
WBC (cell/µl)	14,400	9,500	5,000	
Neutrophils (%)	76	47		
Lymphocytes (%)	21	51		
Monocytes (%)	0	1		
Eosinophils (%)	3	1		
Basophils (%)	0	0		
Hb (%)	10.1	10.9	10.5	11.5
Ht (%)	31.1	34.1		
Plt (cells/µl)	749,000	1,146,000	756,000	372,000
ESR (mm/hr)	125	87		8
ASTO			Negative	Negative
Monospot	Negative			
Urinanalysis	Normal			

WBC: White blood cells, Hb: Hemoglobin, Hto: Hematocrtit, Plt: Platelets, ESR: Erythrocyte sedimentation rate, ASTO: Antistreptolisine

■ DISCUSSION

Kawasaki disease has replaced acute rheumatic fever as the leading cause of acquired heart disease among children in developed countries. The annual incidence of KD in children of Japanese descent is about 150 per 100,000 children younger than five years, and in the United States it affects approximately 10 to 15 per 100 000 children younger than five years.(6) Here in Belize, no other known similar case has been reported through any health system or has probably gone undiagnosed.

Diagnosis relies on clinical criteria and supporting ancillary studies. In our setting, the patient presented himself with the classic (typical) clinical criteria, which include fever for at least five days and four or more of the five major clinical features (i.e., conjunctival injection, cervical lymphadenopathy, oral mucosal changes, swelling or redness of the extremities and desquamation of upper back, elbows and finger tips), and the exclusion of alternative diagnoses. It was also noted that our patient followed the natural history and time course of this disease as portrayed by Paul R. Ogershok's image of the presenting clinical manifestations of KD.(4)

Clinical features may not be present simultaneously, and taking a careful history is necessary in children who lack a clear explanation for fever. If the typical clinical findings are present in a child with fever for less than five days, the diagnosis still can be made by experienced physicians and treatment can be initiated. In addition, classic Kawasaki disease can be diagnosed with three clinical features if coronary artery abnormalities are observed on echocardiography. (6,10) Because many of the clinical features of KD may be present in other illnesses, exclusion of other diseases in the differential diagnosis is often necessary. This was done in our case scenario, where bacterial lymphadenitis was first considered and the patient treated accordingly, as described in the publication by Stamos and Corydon, because it was a prominent feature.(11) Secondly infectious mononucleosis was ruled out by a monospot test.

Apart from the five classic presenting clinical criteria, serial platelet count elevations and desquamation of the skin called our attention to act promptly in the direct management of this patient. During this subacute stage of greatest vascular damage is when a concomitant progressive increase in serum platelet count occurs; being the point of the illness when the risk of death is most significant with a peak mortality occurring 15–45 days after the onset of fever, as depicted in the article by Schenfield and colleagues.(4)

No specific laboratory test is used to diagnose Kawasaki disease; however, certain abnormalities coincide with various stages. Acute-phase reactants such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are almost universally elevated at first; returning to baseline at 6–10 weeks after illness onset.(4) In our setting we had an early full recovery at the fifth week of onset of illness. More recently, two urine proteins hold promise as biomarkers of Kawasaki disease: meprin A or filamin C. These two biomarkers were diagnostically superior to ESR or CRP as depicted by Kentiss and colleagues.(12)

The principal goal of treatment is to prevent coronary artery disease and to relieve symptoms. Full doses of IVIG are the mainstay of treatment. Aspirin (high-dose for a variable period, followed by low-dose) has traditionally been standard, as well. Due to the patient's timely consultation and limited financial resources, IVIG could not be purchased, but instead high dose aspirin was used for one month treatment with two control echocardiograms, which, fortunately for the patient, were normal and eventually of good prognosis.

Many other medications reported in the literature include: corticosteroids: typically in patients unresponsive to standard therapies; methotrexate, cyclophosphamide or

ulinastatin (UTI): in IVIG-resistant cases; infliximab: in refractory cases with coronary aneurysm; antiplatelet medications (eg. clopidogrel, dipyridamole): in patients at increased risk for thrombus with significant coronary involvement; anticoagulants (eg. warfarin, low-molecular-weight heparin): in patients with large aneurysms in whom the risk of thrombus is high.(4)

With these in mind, we highlight the importance of the accurate and timely recognition of this illness that can influence the long-term prognosis of this patient.

■ CONCLUSION

KD is a disease associated with significant morbidity and potential mortality, yet there is no specific diagnostic test available. Increased physician awareness of the dominant clinical features of KD and appropriate use of serial echocardiography in diagnosis have together improved patient prognosis through facilitating timely treatment. Given the severe consequences and sequelae of late diagnosis and the immediate benefits offered by available therapies including IVIG, it is imperative that clinicians consider KD diagnosis in cases of prolonged paediatric fever.

La Enfermedad de Kawasaki, presentación de un caso y revisión bibliográfica: la importancia de su reconocimiento temprano

Resumen

La enfermedad de Kawasaki es una vasculitis aguda de la niñez que afecta predominantemente las arterias coronarias. La causa de la enfermedad de Kawasaki es aún desconocida, aunque existe fuerte sospecha, basada en las características clínicas y epidemiológicas, de que pudieran estar presentes una predisposición genética y un agente infeccioso.

Esta enfermedad, que afecta a niños menores de cinco años, se caracteriza por fiebre prolongada y más de cuatro de los siguientes criterios diagnósticos: erupción polimórfica, conjuntivitis no exudativa, afectación de la mucosa oral, descamación de las extremidades y linfoadenopatía cervical.

Se debe considerar el diagnóstico ante un infante muy irritable y febril con manifestaciones cutáneas.

Debe iniciarse inmediatamente el suministro de inmunoglobulina total endovenosa y aspirina, pilares del tratamiento. El reconocimiento temprano de esta enfermedad es esencial para reducir las complicaciones cardiovasculares como aneurismas y sus secuelas.

Se reporta un caso de un niño de cuatro años diagnosticado y tratado en el Corozal Community Hospital de Belice.

Palabras clave

Enfermedad de Kawasaki, fiebre prolongada, vasculitis, inmunoglobulina endovenosa, aspirina, aneurismas.

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