ABSTRACT
Kawasaki disease (mucocutaneous lymph node syndrome) is a disease of unknown etiology characterized by vasculitis which may affect the coronary arteries. Young children are most commonly affected although the disease has been described in adults. Kawasaki disease (KD) was first described by Dr Tomisaku Kawasaki in 1967. Since then, more cases have been reported worldwide, the majority being from Japan. We report on a 6-year-old child with recurrent attacks of Kawasaki disease which was initially resistant to the conventional treatment.

Key words:
Kawasaki disease; Vasculitis; Coronary arteries aneurysm.

INTRODUCTION
Kawasaki disease (KD) is the commonest cause of acquired heart disease in children in Developed Countries [1]. The diagnosis is based on the presence of at least five of the following six clinical features: 1) persistent fever, 2) polymorphous rash, 3) characteristic changes in the extremities (erythema of the hands and feet followed by desquamation of the fingers and toes), 4) bilateral conjunctivitis, 5) cervical lymphadenopathy, 6) oropharyngeal changes including ‘strawberry’ tongue (prominent lingual papillae), dry, erythematous or cracked lips, and erythema of the oropharyngeal mucosa[2]. Since early diagnosis and treatment is important, the condition should be considered in children presenting with any of the oral features of the disease.

CASE REPORT
A 6-year-old male Saudi child was admitted to Al-Taif Children Hospital, Saudi Arabia, with history of high grade fever, decreased appetite, mild dry cough and loose bowel motion for 7 days. There was no history of vomiting, abdominal pain, respiratory distress or any central nervous system manifestation.
This patient had been admitted at the age of 8 months for 15 days with the diagnosis of KD in the same hospital (high grade fever, swelling of both dorsal hand and feet, cracked lips and erythematous skin lesions). He was treated with intravenous immunoglobulin, aspirin and discharged in good condition with no cardiac complications.
Assessment in this current admission showed an ill looking toxic child who was not pale, cyanosed or...
jaundiced. Both eyes were injected with no discharge. Neck examination showed unilateral small cervical lymph node. No skin rash was observed but he had cracked lips and swelling of dorsal hands and feet (Figure 1). At the time of admission his temperature was 38.7 °C, pulse 140 beats per minute, respiratory rate 30/minute, and oxygen saturation was 98% in room air. The rest of the systemic examination, including the cardiovascular system, respiratory system and central nervous system were unremarkable.

Investigations revealed Hb of 12.9 gm/dl (N 11.5 – 15.5 g/dL), Hct of 28.3% (N 35 – 45%), MCV 79.1 (N 77 – 95 fl), MCH 27.3 (N 25 – 33 pg/cell), MCHC 34.4 (N 31 – 37 %), WBC 15.6 (N 5.5 – 15.5 x 10^9/L), neutrophils 82.6% (N 54 – 62 %), lymphocytes 12% (N 25 – 33%), monocytes 5.3% (N 3 – 7%), eosinophils 0.1% (N 1-3%), ESR 120 (N 0 – 10 mm/hr), platelets 330x10^9 (N 150 – 400 x 10^9), and reticulocyte count 1.8 % (N 0.5 – 1.5%). Peripheral blood film was normal. Serum Na was 134meq/L (N 138 – 145), K 3.6meq/L (N 3.5 – 4.5), Cl 104meq/L (N 98 – 106). Random blood sugar 97.3mg/dl, BUN 14.7 mg/dl (N 20-40 mg/dl), serum creatinine 0.65mg/dl (N 0.3 – 1 mg/dl), Ca 8.35 mg/dl (N 8.8 – 10.8 mg/dl), Mg 0.7mg/dl (N 1.5 – 2.3 mg/dL), PO4 2.74mg/dl (N 3.7 – 5.6 mg/dl), initial bilirubin (total) 0.86mg/dl (N less than 1mg/dl), (repeated 4.4mg/dl, then 0.7mg/dl mostly direct), ALT 35.3 IU/L (N 5 – 45 ), AST 48 IU/L (N 15 – 55 U/L), and alkaline phosphatase 207 IU/L (N 145-420). Chest X-ray and abdominal ultrasound were both were. Blood, urine and throat swab culture showed no growth. Blood culture for fungus was also negative. Viral capsid antigen for EB virus was negative. ASO titre <200
Widal test for typhoid and paratyphoid, and serology for brucellosis were non-significant. Prothrombin time was 15.3 sec (N 11 – 15 sec), and APPT 40 seconds (N 60 – 85 sec). Hepatitis screen, ANA, and DNA double-stranded antibodies were negative. Echocardiography was normal.

The child had persistent high grade remittent fever, remained very ill with no new clinical signs. Cranial CT scan and CSF examination were normal. Initially, he was treated with ceftriaxone and vancomycin. After four days of treatment no response was observed so the diagnosis of Kawasaki disease was suspected. Two doses of Intravenous Immunoglobulin 1 gm / kg/day, for 2 days were given together with acetyl salicylic acid (100 mg/kg/day). Partial response was noticed with fever slightly decreased but still never reached the baseline and the child remained sick. The patient remained very ill-looking, highly febrile and on the eighth day of admission he developed perianal skin excoriation.

Repeated CBC showed Hb of 11.2 gm g/dL (N 11.5 – 15.5 g/dL), Hct 35 (N 35 – 45%), MCV 85.1 (N 77 – 95 fl), MCH 26.9 (N 25 – 33 pg/cell), MCHC 31.9 (N 31 – 37 %), WBC 6040 (N 5.5 – 15.5 x 10⁹/L), N 41.7 (N 54 – 62 %), L 46.4 (N 25 – 33%), E 2.8 (N 1-3%), M 0.7% (N 3 – 7%), Platelets 1140x10⁹ (N 150 – 400 x 10⁹), ESR 125 (N 0 – 10 mm/hr).

The diagnosis of (resistant to treatment) Kawasaki disease was highly suspected at this stage so repeated intravenous immunoglobulin infusion of 1gm/kg/day for two days was initiated. Both salicylate and intravenous antibiotics were continued. Dramatic response was noticed after the first dose of immunoglobulin. The patient became afebrile, so salicylate was decreased to 5 mg/kg /day and antibiotic discontinued. Repeated echocardiography showed slightly dilated coronary arteries at the upper limit of normal compared to the finding in the initial echocardiogram. Patient was discharged home in good condition and remained well on follow up.

**DISCUSSION**

Kawasaki disease (KD) is predominately a disease of childhood although cases have been reported in adults [3]. Around 80% of cases occur in children under 5 years of age [2]. It occurs more often in boys than girls with a male to female ratio of about 1.5:1. Cases have been reported worldwide in children of all racial background. Kawasaki disease remains uncommon. It is possible that cases are missed, because many common childhood infections have similar clinical features [1].

The differential diagnosis of KD includes streptococcal infection, staphylococcal infection, measles, juvenile rheumatoid arthritis and drug reactions. High index of suspicion is required to diagnose atypical cases which lack some of the classical signs. Some cases are only diagnosed after the characteristic coronary artery changes have been found on echocardiography or at necropsy [4]. Also, high degree of suspicion is required in patients who have a previous history of Kawasaki disease and present with clinical signs consistent with recurrence with failure to respond to antibiotics as in our patient. The coronary artery aneurysms occur in around 20-30% of untreated cases [5]. Up to 4% of cases of untreated Kawasaki disease will progress to sudden death during the acute phase of the illness as a result of aneurysmal thrombosis formation, myocardial infarction or dysrhythmia [6]. While many aneurysms appear to resolve spontaneously, long term morbidity can result from scaring of cardiac tissue. In about 1% of cases the heart valves are affected [7], in which case antibiotic prophylaxis against infective endocarditis will be necessary prior to relevant dental procedures in the future.

The etiology of Kawasaki disease remains obscure. Epidemiological evidence suggests a microbial agents as the likely cause, however no causative organism has been identified to date [1]. Regardless of etiology, early treatment with a single dose of intravenous immunoglobulin (2 gm/kg) has been shown to significantly reduce the incidence and severity of aneurysm formation as well as providing symptomatic
relief for the acute illness [8]. Immunoglobulin appears to be the most beneficial if given as early as possible after diagnosis [2]. Low dose aspirin is also used for its anti-inflammatory and anti thrombotic effects although its efficacy remains unproven. Paracetamol can also be used as an anti-pyretic. Recurrence of KD has been previously noted with reported rates varying between 0.8% in the united states to 3% in Japan [8,9]. The proportion of patients suffering a recurrence increase with age, while the majority of recurrence occurs within 2 years of the initial attack [9]. In rare cases (0.2%), patient can suffer multiple recurrences [9]. Interestingly, the only factor so far identified which predispose to recurrence is previous treatment with immunoglobulin [10]. The clinical symptoms of recurrent KD were incomplete in children. Recurrence can be more serious than that of the first attack and the complication rate of coronary arterial lesion is higher in the second attack. In 10 to 15% of patients with KD who are initially treated with IVIG and aspirin, fever persists or returns within 48 hours [11,12] . Persistent fever of any magnitude is generally assumed to be caused by ongoing vasculitis, although other causes of fever such as reaction to intravenous immunoglobulin therapy and intercurrent infection should be considered. Patients who remained febrile after treatment had an almost nine folds increase risk of developing coronary arteries abnormalities compared to those who responded to initial IVIG (12.2 versus 1.4 percent) [11]. Children who are febrile more than 36 hours after the completion of their initial IVIG infusion require additional therapy. The second dose intravenous immunoglobulin infusion is safe and well tolerated in the subject with KD who was resistant to standard IVIG treatment. The optimal management of patients resistant to IVIG remains to be determined [13]. Another option of treating resistant cases with KD who do not respond to intravenous immunoglobulin is to treat with high dose of methylprednisolone (30mg / kg per day) for 1 to 3 days period [14]. Infliximab is a monoclonal antibody against tumor necrosis factor alpha (TNFα), used to treat autoimmune disease, is now used for treatment of resistant Kawasaki disease. Both infliximab and a second IVIG infusion were safe and well tolerated in patients with Kawasaki disease resistant to standard IVIG treatment [13, 15].

REFERENCE

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