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Peripheral Gangrene Associated with Kawasaki Disease and Successful Management Using Prostacycline Analogue: A Case Report

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ABSTRACT

We report a case of child-onset Kawasaki disease that presented as a prolonged fever and manifested with coronary aneurysms and peripheral gangrene of the lower limbs. Therapy with intravenous immunoglobulins, corticosteroids, aspirin, anticoagulants, and ilomedine, a prostacyclin analogue, resulted in rapid improvement in the patient's condition without extremity loss. Those treating patients with Kawasaki disease must be aware of possible vascular ischemia in the disease process that is reversible by early intervention treatments, including the use of a prostacycline analogue, that improve quality of life.

INTRODUCTION

Kawasaki disease (KD) is an acute, self-limited vasculitis of unknown etiology that occurs predominantly in infants and young children [Newburger 2004]. KD is characterized by fever, bilateral nonexudative conjunctivitis, erythema of the lips and oral mucosa, changes in the extremities, rash, and cervical lymphadenopathy [Newburger 2005]. KD is the leading cause of acquired heart disease in the developed world [Burns 2004]. When high-dose intravenous immunoglobulin and aspirin therapy have been applied as treatment, 15% to 25% of KD patients have had complications of coronary arterial aneurysm and fever; 1% died because of myocardial infarction or myocarditis [Newburger 2004]. In this report, we describe the case of 7-year-old girl with KD who developed severe lower limb peripheral gangrene during the acute phase of the illness. Because her condition was not improved by an initial treatment that included antiplatelet, anticoagulation, dextran, and steroid administration, we started ilomedine, a potent vasodilator. Total cure of the limb ischemia was provided without a need for extremity amputation. As a result, we would like to present this case to point out a favorable outcome of severe ischemia associated with KD that was managed by prostacycline, dextran, and steroid treatment.

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CASE REPORT

A 7-year-old girl was transferred to the Hacettepe University Ihsan Dogramaci Children's Hospital with persistent fever associated with a rash for 6 days. The patient's temperature was 39.5°C at admission, and physical examination revealed nonexudative conjunctivitis, red lips and a strawberry tongue, and erythema of her hands and feet with bluish discoloration at the tips of her left toes. She also had pain in her toes. Laboratory studies showed normal hemoglobin (12.7 mg/dL) and thrombocytosis (470.000/mm^3) levels. An echocardiogram showed dilation on the right and left coronary arteries (5 and 6 mm, respectively; Figure 1); a diagnosis of KD was made and the patient was given intravenous immunoglobulin and high-dose aspirin (80 mg/kg per day). After completion of a full 2 g/kg dose of intravenous immunoglobulin, the ischemia in her left toes was still worsening. She was given a steroid (deltacortil, 30 mg/day), dextran 40 10% (150 cc infusion over 6 hours/day), betahistine (8 mg, 3 times per day), and aspirin with heparin infusion 15 to 20 U/kg per hour to keep the partial thromboplastin time at more than 1.5 times the control. Despite the initial treatment, unfortunately, the left distal limb ischemia and necrosis did not improve. Within 10 days, her toes got better but the distal digital acrocyanosis became well demarcated. Steroid treatment was stopped gradually, and dextran treatment was discontinued (Figure 2). With the administration of antiaggregant and anticoagulant treatment, we administrated ilomedine, a very potent vasodilator prostacycline analogue, at a daily dose of 2 ng/kg. Five days later, the pain in her left toes had improved, and 7 days later the digital necrosis had totally disappeared (Figure 3). The ilomedine infusion was continued for 21 days.

Tests to rule out the presence of another childhood vasculitis anti-nuclear antibody, pANCA, were negative; compleman 3 and 4 levels were within the normal range; and results of magnetic resonance imaging angiography studies of both the abdomen and cranium were normal. Also, Doppler ultrasonagraphic examinations of the kidney and iliac and popliteal arteries were normal. The patient was discharged from the hospital with the administration of aspirin

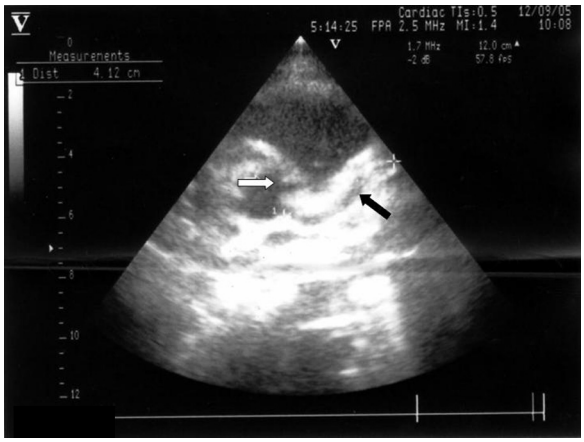

Figure 1. Two-dimensional echocardiography shows the coronary artery dilation at the time of admission.

and dipyridamole. The patient remained afebrile during the hospitalization period, and at the 2-month follow-up there was no circulation problem in the toes. Echocardiography revealed left and right coronary enlargement with distal 3.3-mm and 4.1-mm aneurysms, and her aspirin therapy has been continued.

DISCUSSION

KD is an acute systemic vasculitis of childhood that primarily affects the coronary arteries [Newburger 2004]. Patients in whom coronary aneurysms develop are at risk for myocardial ischemia and infarction, and mortality from KD virtually always results from ischemic myocardial disease. Clinical features affecting many systems are documented in the literature and may be present at the diagnosis or develop during the illness [Tizard 2005]. However, the complication of peripheral limb ischemias or gangrene has been reported very rarely [Tomita 1992; Waldron 1993; Chang 1999; Krohn 2001]. Fourteen cases have been presented in the literature [Tomita 1992; Waldron 1993; Chang 1999; Krohn 2001], and as noted by Chang et al, only 3 of them were Asian children, although the incidence of KD is at least twice as high as in Caucasians [Chang 1999]. There is only one adult case with

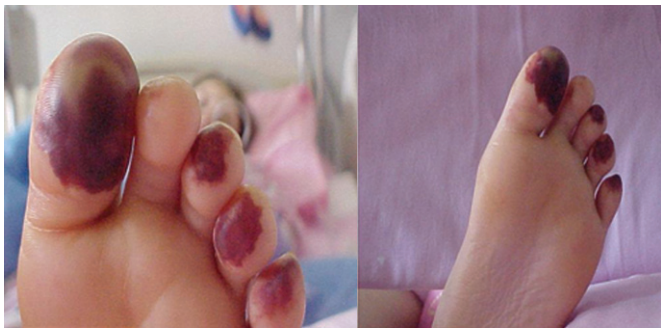

Figure 2. After the initial treatment, well-demarcated digital lesions at day 10 are seen.

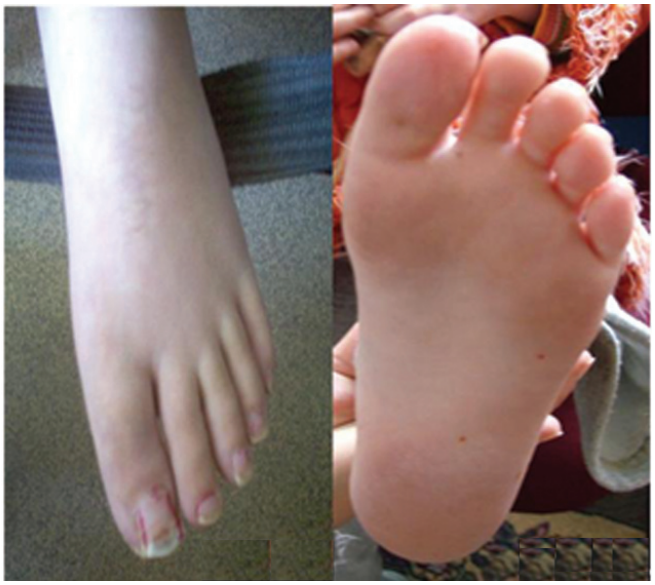

Figure 3. After the administration of prostacycline infusion, the ischemic lesions on the toes have disappeared at day 21.

extremity necrosis or ischemia treated by the administration of prostacycline analogue in the literature [Bonte 2005]. We present for the first time a female child who was treated successfully with prostacycline analogue.

Because the described drug is a very potent vasodilator, prostacycline intravenous infusion has been proposed especially in cases with pulmonary hypertension [Dogan 2004] or atherosclerosis obliterans [Brodmann 2000]. Despite the aggressive treatment strategy in a limited number of cases, extremity amputation has been reported in many reports in the literature. As has since been reported by others [Chang 1999; Krohn 2001], Trumble et al reported 2 cases with extremity necrosis caused by KD [Trumble 1986]. In these cases, despite the use of an anticoagulant agent, hyperbaric oxygen therapy, and steroid administration for the treatment of extremity necrosis, both patients required extremity amputation.

Approximately 20% to 25% of untreated patients with KD develop coronary artery abnormalities, including aneurysm and diffusion dilation, and fewer than 1% die because of myocardial infarction or myocarditis [Newburger 2004]. The high-dose intravenous immunoglobulin therapy is believed to be effective in preventing complications of KD if it is administered during the acute stage [Newburger 1991].

All of the previous cases of KD with peripheral ischemia were of patients younger than 1 year of age, and they eventually suffered from serious complications. The presented patient was 7 years old and, aside from being the oldest case in the literature, it is also the only case that was without any severe complications except for mild coronary dilatation. The pathogenesis of peripheral ischemia in KD might be the same as that of coronary arterial aneurysm or stenosis.

In conclusion, distal ischemia due to a peripheral vasculitic form in KD may be seen in children or adults. However,

peripheral ischemia leading to gangrene is a very rare feature of KD. We report on a 7-year-old patient with KD who presented with distal limb ischemia due to vasculitis, manifested by coronary aneurysms. The initial therapy included intravenous immunoglobulin, corticosteroid, aspirin, and anticoagulants; however, clinicians should consider using prostacyclin analogue in the treatment strategy because, in a number of cases, the clinical results were very poor with the classic treatment approach and led to distal amputation. As we have shown, rapid improvement in the patient's condition might be obtained by ilomedine treatment.

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