Kawasaki Disease Complicated by Peripheral Gangrene in a Case of Inherited Thrombophilia

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Abstract

Kawasaki disease is a febrile vasculitis targeting medium sized arteries, causing coronary artery aneurysm without appropriate treatment. Many children do not fulfill the criteria and due to its serious complications, the American Heart Association (AHA) published an algorithm for atypical Kawasaki disease based on laboratory tests and echocardiography. Peripheral ischemia is a rare complication with harmful sequelae. Here we report a case of a 14-month-old patient, who was diagnosed of atypical Kawasaki disease, developed peripheral ischemia and gangrene of the second and third right hand fingers, and was found to have factor V Leiden heterozygous mutation.

Keywords: Kawasaki; Gangrene; Thrombophilia; Factor V Leiden; Ileal atresia

Introduction

Kawasaki disease is an acute systemic vasculitis primarily affecting infants and young children. Twenty percent of children with this disease who do not receive intravenous gamma globulin (IVIG) therapy develop coronary artery aneurysms [1]. Peripheral ischemia and necrosis are rare and harmful complications, which are reported mainly below age of 1 year. We describe here a case of a 14-month-old male, who was diagnosed of atypical Kawasaki disease, developed peripheral ischemia and gangrene of the second and third right hand fingers, with factor V Leiden heterozygous mutation.

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IVIG was given (2 g/kg), aspirin (100 mg/kg/day), prostaglandin E1 infusion (0.02 mcg/kg/min), enoxaparin (1 mg/kg/dose) every 12 h, fresh frozen plasma once daily, broad spectrum antibiotics, meropenem (40 mg/kg/dose) and vancomycin (20 mg/kg/dose) for 14 days, and pulse steroid therapy (30 mg/kg) given for 3 days.

On day 10, the patient had a significant increase in swelling associated with severe pain; thus, fasciotomy was done to relieve his compartment syndrome, and swab culture was taken which revealed no growth.

Coagulation profile showed normal international normalized ratio (INR), partial thromboplastin time (PTT), protein C, anti-thrombin III, fibrinogen, low protein S and D-dimer, and factor V Leiden heterozygous mutation.

Repeated echocardiography in 2 weeks was normal, and CT scan angiography of the right upper limb showed patent vessels (Fig. 2). The patient was discharged home on enoxaparin and aspirin, and was followed up by plastic surgeon; dry dressing was applied and the anti-factor Xa was monthly monitored to maintain a therapeutic range (0.5 - 1.0 unit/mL) of enoxaparin. Unfortunately, autoamputation of the second and third right fingers finally took place after 5 months (Fig. 3).

**Discussion**

Herein we report a case of patient with atypical Kawasaki, who developed peripheral ischemia of second and third fingers of right hand, a rare complication, and was found to have factor V Leiden heterozygous mutation that increases the risk of coagulopathy and thrombosis.

Early diagnosis and treatment of Kawasaki disease is important; however, an atypical form of Kawasaki disease is now well understood. To facilitate the diagnosis of incomplete or atypical Kawasaki disease, the algorithm recently published by the American Heart Association (AHA) [2, 3] calls for measurement of C-reactive protein and ESR on day 5 of fever in patients with 2 or 3 of the clinical criteria for Kawasaki disease. Patients found to have a C-reactive protein level of 3.0 mg/dL and/or an ESR of 40 mm/h are advised to undergo supplemental laboratory testing and an echocardiogram. Patients meeting 3 or more of the supplementary laboratory criteria (albumin 3.0 g/dL, anemia for age, elevated alanine aminotransferase, platelets after 7 days 450,000/mm³, white blood cell count 15,000/mm³ and urine 10 white blood cells/high-power field) or with a positive echocardiogram should be treated with IVIG for Kawasaki disease [3].

This latter aspect of the algorithm is designed to “increase the sensitivity while maintaining sufficient specificity,” given the potential serious complications of the disease and the safety and efficacy of early treatment [3]. We have identified 14 other case reports of peripheral gangrene in patients...
with Kawasaki disease. The median age of these patients with gangrene is 3 months [4]. Possible pathogenic mechanisms of peripheral gangrene include severe arteritis of digital or other peripheral small arteries; arteriospasm of peripheral small-to-medium-sized arteries, perhaps in association with severe vasculitis; thrombosis of inflamed or spastic small to medium-sized arteries as a result of stagnant blood flow and damaged endothelium; and thrombosis of a more proximal arterial aneurysm with embolism distally [5]. The median time was 15 - 31 days after the onset of illness for the clinical signs of peripheral ischemia and gangrene to manifest in the previously reported cases, despite initiating anti-inflammatory therapy [5].

There is no consensus regarding the ideal therapy for the peripheral ischemia in the aforementioned case reports [4]. In our case, it appeared that IVIG, high-dose aspirin, enoxaparin and pulse steroid therapy were most helpful in controlling the inflammatory process, and the fever resolved soon after initiation of these therapies.

The etiology of congenital atresia involving the jejunum, ileum and colon has long been thought to result from an in utero mesenteric vascular accident [6]. In 1912, Spuggs suggested that mechanical accidents, including vascular accidents, might be responsible for intestinal atresia [7]. An increased risk of thrombotic disease recently has been described in association with inherited thrombophilia, defined as a genetically inherited tendency towards spontaneous vascular thrombosis [8]. Before 1993, the chance of discovering a definable thrombophilia in patients with a thrombotic event was as low as 5-15% [6]. Thus, the chance of discovering an association between thrombophilia and a birth defect was extremely unlikely [9]. This has changed over the past few years with the discovery of numerous genetically transmissible factors that are known to predispose to thrombotic disease. Of these inherited thrombophilias, the best described and most common condition is referred to as factor V Leiden. The factor V Leiden mutation predisposes to thrombosis because of a loss of the anticoagulant properties of protein C, which normally limit the coagulation cascade [10]. The pathophysiological mechanism by which activated protein C (APC) resistance occurs is related to an inherited abnormality of factor V rather than an intrinsic abnormality in APC. Among heterozygotes, thrombosis occurs at a rate of 5 - 10 times that of the unaffected population (as our patient); with homozygotes, thrombosis occurs 50 - 100 times more frequently [11].

In conclusion, peripheral limb gangrene is a rare complication of Kawasaki disease, which needs to be early recognized and treated with every effective treatment including anti-inflammatory and anti-thrombotic drugs. We should search for inherited thrombophilias that might have an add-on role in the peripheral gangrene, and further aggressive treatment with plasma and factors replacement, to minimize the sequelae.

Conflict of Interest

The authors declare that they have no conflict of interest.

Consent

Written informed consent was obtained from the patient’s family for publication of this case report and accompanying images.

References