Case Report

Infliximab as a Novel Therapy for Refractory Kawasaki Disease

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ABSTRACT. Kawasaki disease (KD) is a multisystem vasculitis of unknown etiology, with coronary artery aneurysms occurring in 25% of untreated cases. With conventional treatment of intravenous immunoglobulin (IVIG) and high dose aspirin (ASA) only 4% of patients develop coronary artery aneurysms. Children who are unresponsive present a challenge. Tumor necrosis factor-α levels peak during the acute and subacute phase of KD, especially in children who develop coronary artery aneurysms. We describe a 3-year-old male with KD and giant coronary artery aneurysms, unresponsive to multiple doses of IVIG and methylprednisolone, who was treated with infliximab. After the first dose he defervesced and his laboratory measures improved. (J Rheumatol 2004;31:808–10)

Key Indexing Terms:
KAWASAKI DISEASE
CORONARY ARTERY ANEURYSM
TUMOR NECROSIS FACTOR-α
INFLIXIMAB

Kawasaki disease (KD) is a multisystem vasculitis of unknown etiology, with coronary artery aneurysms occurring in 25% of untreated cases. Only 4% of patients develop coronary artery aneurysms with conventional treatment of intravenous immunoglobulin (IVIG) and high dose aspirin (ASA)[1,2]. There is no other effective treatment for children who do not respond to conventional therapy. Tumor necrosis factor-α (TNF-α) concentrations are at their peak during the acute and subacute phase of the disease, especially in children who develop coronary artery aneurysms[3,4]. The immune response to TNF, interleukin 1 (IL-1), and other cytokines results in weakening of the endothelial wall, promoting aneurysm formation[5]. An anti-TNF-α agent could theoretically lower the systemic TNF-α concentrations, thereby halting the vasculitis and the progression of coronary artery aneurysm.

We successfully treated a patient with KD and giant coronary artery aneurysms, refractory to conventional therapy, with infliximab based on this hypothesis.

CASE REPORT

A 3-year-old white male was diagnosed with KD after presenting with fever for 10 days, an erythematous rash, subcutaneous edema of his hands, bilateral conjunctivitis, dry cracked lips, and an erythematous tongue. Laboratory measures were significant for thrombocytosis and an elevated erythrocyte sedimentation rate (ESR). Initial echocardiogram was normal. He was treated with IVIG (2 g/kg) and ASA (80 mg/kg/day) and defervesced for 24 h, but then required a second treatment of IVIG due to recurrent fever. He was discharged afebrile taking low dose aspirin.

He was readmitted 4 days later with fever and a desquamating rash of his digits. Laboratory results were significant for anemia, thrombocytosis, elevated ESR, elevated liver enzymes, and low albumin. At this time, his echocardiogram was significant for a saccular aneurysm of the left coronary artery (5–6 mm) with ectasia of the anterior descending and circumflex arteries and a proximal tubular aneurysm of the right coronary artery (8–9 mm). Throughout his 50-day hospital course he received a total of 8 doses of IVIG, 8 pulses of methylprednisolone, and daily oral prednisolone, with fever recurring 1–2 days after each treatment. ESR, platelet count, and liver enzymes remained elevated and he remained anemic and with a low albumin. Repeat echocardiograms showed continuous progression of his coronary artery aneurysms, with the left coronary artery aneurysm measuring 8.7 mm (Figure 1) and the right coronary artery aneurysm measuring 11 mm (Figure 2). At this time there was also evidence of a small pericardial effusion. Since all interventions failed to control his systemic inflammation he was treated with infliximab (5.0 mg/kg) using the rheumatoid arthritis protocol (on Days 45, 59, and 89) with a good response. He had no further fever following the first infusion and his pericardial effusion resolved. Inflammatory markers began to decrease and remained normal thereafter.

DISCUSSION

The pathogenesis of vascular injury and aneurysm formation in acute KD is associated with elevated serum concentrations of IL-1, TNF, and interferon-γ, as these cytokines cause expression of neo-antigens on endothelial cells, rendering them susceptible to cytotoxic antibodies secondary to polyclonal activation. It has also been shown that sera from patients during the acute phase of KD causes complement-mediated killing of endothelial cells stimulated by IL-1 or TNF. This immune response leads to damage of the vessel wall and aneurysm formation[5-7].

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Submitted February 14, 2003; revision accepted October 6, 2003.

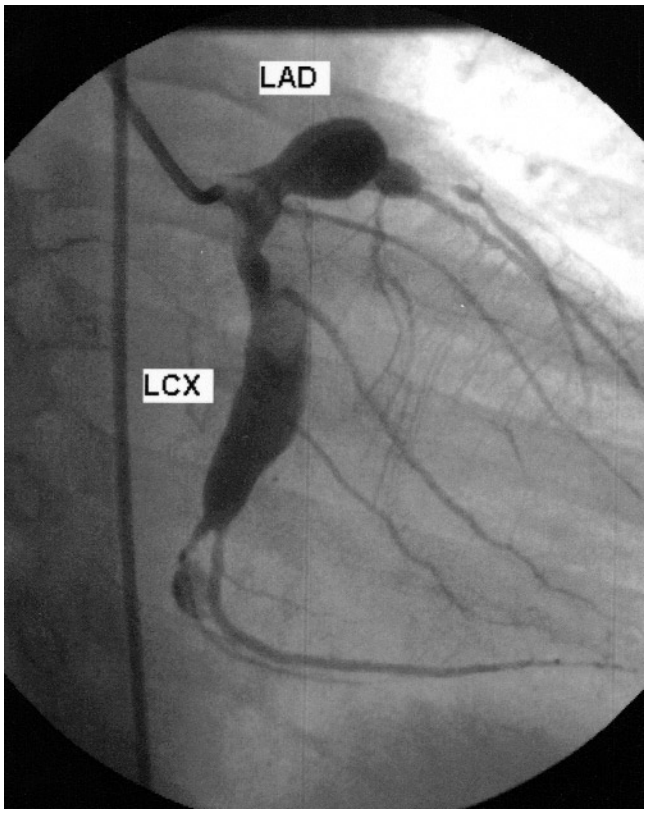

Figure 1. Left main coronary artery. A saccular aneurysm of the left anterior descending (LAD) artery measuring 8.7 × 11 mm diameter and another small aneurysm measuring 2 mm diameter. A saccular, fusiform aneurysm of the left circumflex artery (LCX) measuring 35 × 8 mm diameter. The distal circumflex artery had another small aneurysm with an area of proximal stenosis.

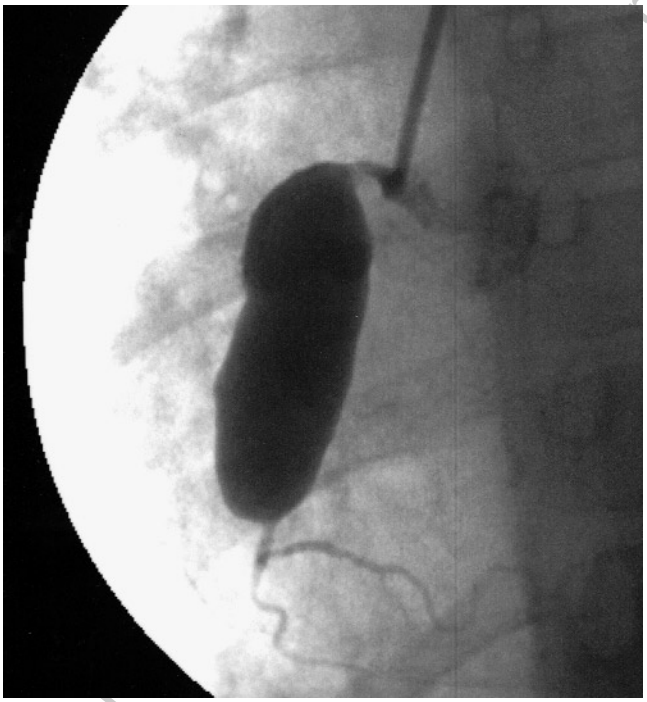

Figure 2. Right coronary artery aneurysm. A giant fusiform aneurysm of the right coronary artery measuring 11 × 31 mm diameter.

Infliximab is a chimeric mouse/human monoclonal antibody that effectively downregulates TNF-α concentrations and controls disease activity in illnesses associated with aberrant secretion of TNF-α. Adverse events include infusion reactions, sepsis, and possible reactivation of tuberculosis[8,9].

Numerous studies have reported elevation of TNF and other inflammatory cytokines during the acute phase of KD. In one study, 39 children with KD, all treated with ASA, and 21 treated with IVIG (400 mg/kg/day × 5 days) gave serum samples during all phases of the disease. Aneurysms developed in 4/39 patients, those with the highest TNF levels during the acute phase. TNF-α levels were found to be significantly higher in the first 3 weeks of illness compared to the convalescent phase and compared to controls[3]. Matsubara, *et al* also found in their prospective study of 45 patients with KD that 17/45 (37.8%) had elevated TNF levels, and of the 11 patients that developed aneurysms, 10 (90%) had significantly elevated TNF levels compared to those without aneurysms (7/34, 20.6%)[4].

The use of steroids in patients with KD has remained controversial since Kato, *et al* reported that patients treated with prednisolone developed coronary artery aneurysms[10]. Pulse methylprednisolone (30 mg/kg) for 1 to 3 days has also been used, although safety remains an issue, as coronary artery dilatation has been seen during the infusion[11,12]. Indeed, in our patient there was concern regarding the ability of the aneurysms to heal given the amount of methylprednisolone he received.

We describe a patient with refractory KD complicated by giant aneurysms who was treated with a course of infliximab. After the first dose of infliximab, he defervesced, inflammatory markers began to decrease, and the pericardial effusion resolved. We suggest infliximab may be an effective adjuvant therapy in patients refractory to repeated treatments with IVIG and/or corticosteroids. Since this patient was treated, 2 additional children with refractory KD and coronary artery aneurysms have received single doses of infliximab at our institution. All children experienced resolution of their fever, normalization of inflammatory markers, and no further progression of coronary artery aneurysms. A prospective, randomized trial examining the use of infliximab in patients with KD refractory to IVIG is necessary to establish its efficacy in this disease.

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