□ Case Report □

Infliximab treatment for a patient with refractory Kawasaki disease

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Intravenous immunoglobulin (IVIG) infusion is an effective therapy for acute Kawasaki disease (KD). Nonetheless, approximately 10 percent to 20 percent of patients have persistent or recrudescent fever despite IVIG treatment, leading to a higher risk for coronary artery aneurysms (CAA). This unresponsiveness may pose a challenge to the clinicians. Tumor necrosis factor-α levels are elevated in the acute phase of the disease, especially in patients who develop CAA. We report a 10-month-old male with KD who failed to respond to multiple doses of IVIG and methylprednisolone and who then was treated with infliximab (5 mg/kg single dose). After infliximab treatment, he became afebrile with normalization of inflammatory markers and no further progression of CAA. **(Korean J Pediatr 2006;49:987-990)**

Key Words : Mucocutaneous lymph node syndrome, Tumor necrosis factor-α, Infliximab

Introduction

Intravenous immunoglobulin (IVIG) infusion is an effective therapy for acute Kawasaki disease (KD) as it reduces the duration of fever and the prevalence of coronary artery aneurysms (CAA)[1]. Nonetheless, approximately 10% to 20 % of patients have persistent or recrudescent fever after IVIG treatment, leading to a higher risk for CAA[2]. For these patients, current practice is to administer additional therapies, such as repeated doses of IVIG[3], pulse methylprednisolone[4], cyclophosphamide[5], methotrexate[6] or plasmapheresis[7]. Tumor necrosis factor (TNF)-α levels are elevated in patients with acute KD, with the peak levels observed in patients who develop CAA[8]. It is postulated that a TNF-α blockade lowers the systemic TNF-α levels, thereby controlling the vasculitis and the progression of CAA. Recently the use of infliximab, a TNF-α blockade, was reported in patients with refractory KD[9].

We describe here a KD patient who failed to respond to conventional therapy, but was successfully treated with infliximab.

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Case report

A 10-month-old male was diagnosed with KD after presenting with fever for two days, bilateral conjunctivitis, dry cracked lips, an erythematous rash, subcutaneous edema of hands and feet, cervical lymphadenopathy and erythema at the BCG site.

At admission, his general condition was poor with pyrexia (39.3℃) and tachycardia (134/min). There was no leukocytosis (11,000/mm^3) with 78% neutrophils, 19% lymphocytes and the platelet count was 232,000/mm^3. The erythrocyte sedimentation rate (ESR) was 11 mm/hr and the C-reactive protein (CRP) level, 4.1 mg/dL. The N-terminal fragment of B-type natriuretic peptide (NT-proBNP) level was highly elevated to 7,251 pg/mL (normal, <260 pg/mL[10]) (Table 1). Aspartate aminotransferase/alanine aminotransferase were 298/426 IU/L. The initial echocardiogram showed dilatation of the left anterior descending coronary artery (LAD) (2.4 mm, z=2.4[11]) and normal right coronary artery (RCA) (Fig. 1A).

The patient was immediately treated with IVIG (2 g/kg) and salicylate (100 mg/kg/day) but was unresponsive and required a second treatment of IVIG and additionally three doses of pulse methylprednisolone (30 mg/kg/dose intravenously) due to persistent fever. He remained febrile fol-

Table 1. Changes in Coronary Artery Diameter and Laboratory Measures

Illness Day	3	5	10	17	90	160
Hospital Day	1	3	8	15		
LAD (mm/z value)		2.4/2.4	3.2/4.7	4.6/8.6	3.2/4.7	2.9/3.8
RCA (mm/z value)		2.0/0.7	2.7/2.5	4.3/6.5	3.3/4.0	2.6/2.2
ESR (mm/hr)	11		39	37		
CRP (mg/dL)	4.1		4.3	<0.3		
NT-proBNP (pg/mL)	7,251		847	187		

Abbreviations : CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LAD, left anterior descending coronary artery; NT-proBNP, N-terminal fragment of B-type natriuretic peptide; RCA, right coronary artery

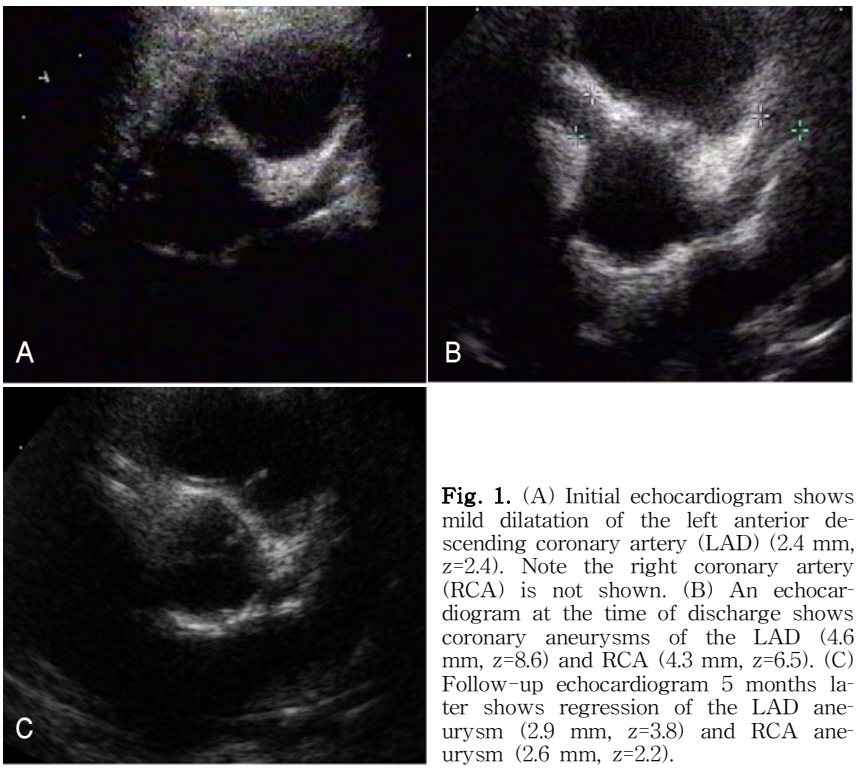

Fig. 1. (A) Initial echocardiogram shows mild dilatation of the left anterior descending coronary artery (LAD) (2.4 mm, z=2.4). Note the right coronary artery (RCA) is not shown. (B) An echocardiogram at the time of discharge shows coronary aneurysms of the LAD (4.6 mm, z=8.6) and RCA (4.3 mm, z=6.5). (C) Follow-up echocardiogram 5 months later shows regression of the LAD aneurysm (2.9 mm, z=3.8) and RCA aneurysm (2.6 mm, z=2.2).

lowing these treatments. The ESR increased to 39 mm/hr. The CRP and NT-proBNP remained elevated (4.3 mg/dL and 847 pg/mL, respectively). Repeat echocardiogram showed continuous progression of coronary artery dilatation, with the LAD measuring 3.2 mm (z=4.7) and the RCA measuring 2.7 mm (z=2.5). Since all interventions failed to control his systemic inflammation, he was treated with a single infusion of 5 mg/kg of infliximab (Remicade, Centocor, Malvern, Pa, Holland) on hospital day 8 (illness day 10). At 40 hours after infusion, he became persistently afebrile (Fig. 2). The CRP decreased to <0.3 mg/dL and the NT-proBNP normalized to 187 pg/mL. There were no complications related to infliximab infusion. The patient was discharged afebrile taking low dose aspirin on hospital day 15 (illness day 17) with the aneurysms of the LAD (4.6 mm, z=8.6) and RCA (4.3 mm, z=6.5) (Fig. 1B).

During follow-up, the patient has been doing well with no evidence of recrudescence of the disease. An echocardiogram 3 months after discharge revealed the regression of the CAA, with the LAD aneurysm measuring 3.2 mm (z=4.7) and the RCA aneurysm measuring 3.3 mm (z=4.0). The latest echocardiogram 5 months postdischarge showed the more regressed aneurysms of the LAD (2.9 mm, z=3.8) and RCA (2.6 mm, z=2.2) (Fig. 1C).

Discussion

Although IVIG plus aspirin therapy is effective for

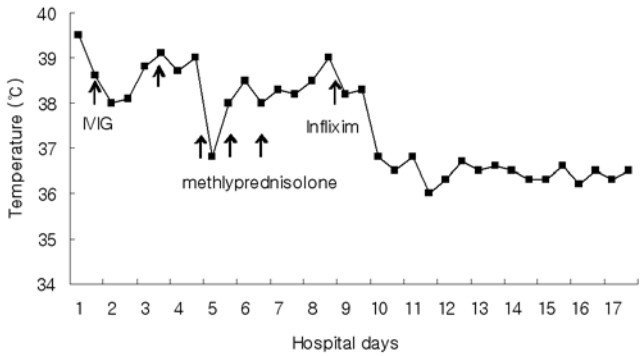

Fig. 2. Changes in body temperature and types of intervention. After infliximab infusion, the patient refractory to repeated treatment with immunoglobulin (IVIG) and pulse methylprednisolone becomes persistently afebrile.

treatment of acute KD[1], approximately 10% to 20% of patients are resistant to this treatment, leading to a higher risk of developing CAA[2]. We reported that coronary artery abnormalities developed in 9 of 20 (45%) patients unresponsive to the first IVIG infusion and in only 21 of 154 (13.6%) patients who responded to a single IVIG treatment[12]. For treatment of IVIG-resistant patients, a variety of therapies including repeated doses of IVIG[3], high-dose pulse methylprednisolone[4], cyclophosphamide[5] or methotrexate[6] has been tried but there is no established guideline for the choice of treatment.

TNF-α levels are markedly elevated during the acute phase of KD and the degree of elevation correlates with coronary artery damage and the development of CAA[8]. Therefore, it is postulated that TNF-α blockades lower the systemic TNF-α levels, thereby controlling the vasculitis and the progression of CAA. Actually, the pathogenesis of vascular injury may result from the endothelial damage induced by TNF-α and other inflammatory cytokines[13]. Infliximab is a chimeric murine/human immunoglobulin G1 monoclonal antibody that binds specifically to human TNF-α1[14] and controls disease activity by down-regulation of TNF-α concentrations.

Regarding the use of infliximab for KD, there are a single case report describing clinical improvement in a patient with refractory KD[15] and also a multicenter clinical trial in 17 patients with refractory KD showing dramatic response to infliximab with cessation of fever in 14 of 16 patients[9]. In this case report, we also describe a patient with refractory KD who was successfully treated with infliximab. After infusion, defervescence was noted and inflammatory markers were decreased. The cessation of fever and lowering of CRP level following TNF-α blockade supports the claim that TNF-α may be a central mediator for this type of vasculitis. We suggest infliximab may be an effective therapy in patients refractory to repeated treatment with IVIG and/or corticosteroids. A prospective, randomized clinical trials will establish the efficacy of TNF-α blockade in patients with refractory KD.

한 글 요 약

Infliximab으로 치료한 난치성 가와사끼병 1례

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정맥내 면역글로블린은 급성 가와사끼병의 치료에 효과적이나 약 10-20%의 환자에서 치료 실패가 보고되고 있다. 이러한 경우 면역글로블린의 재투여 또는 스테로이드나 다른 약제의 사용 등 다양한 치료방법이 시도되고 있으나 아직 이에 대한 확립된 치료 가이드라인은 없다. TNF-α는 가와사끼병의 급성기, 특히 관상동맥류를 가진 환자에서 혈중농도가 크게 증가한다. 저자들은 2번의 면역글로블린 투여와 3번의 pulse methylprednisolone 치료에 반응이 없던 10개월 된 난치성 가와사끼병 환아에게 항 TNF-α인 infliximab (5 mg/kg, 1회)을 투여하여 임상 호전과 더불어 항염증지표가 정상이 되고 관상동맥류 진행이 억제됨을 경험하였다.

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