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Case Report

A Case of Intravenous Immunoglobulin-Resistant Kawasaki Disease Treated with Methotrexate

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Kawasaki disease, an acute febrile vasculitis of unknown etiology, is usually treated with high doses of immunoglobulin (IVIG) and aspirin. However, 20% of children show persistent or recurrent fever despite IVIG, and coronary artery aneurysm progression. In such cases of resistance to IVIG treatment, repeated IVIG administration or the initiation of steroid therapy, and the use of cyclophosphamide have been reported. We aimed to show in this study that methotrexate (MTX) may be used as a treatment for Kawasaki disease resistant to IVIG treatment.

We report the case of a 6-year old boy who was admitted at another hospital with an initial complaint of a fever for 5 days and skin rashes for 3 days. The patients fever persisted despite three courses of IVIG (2 gm/kg, 1 gm/kg, 1 gm/kg, respectively) over a 14-day period. On day 14 of his illness he showed a dilated right coronary artery, and on day 19 dexamethasone, at a daily dose of 0.3 mg/kg, was given but this resulted in defervescence. However, upon stopping the dexamethasone treatment, his fever recurred and he was transferred to our hospital. On days 31 and 38 of his illness, IVIG (400 mg/kg for 5 days, twice) was administered and from day 38 onwards the patient was given dexamethasone (0.6 mg/kg, daily) and MTX (10 mg/BSA, once weekly) whereupon his fever subsided and did not recur. On day 48 dexamethasone was replaced with prednisolone, which was subsequently tapered. The patient is now taking MTX and being observed on an outpatient basis.

We report the case of a boy with IV-globulin resistant Kawasaki disease, who after repeated infusions of IVIG and steroid therapy showed fever recruuence, which that subsided after MTX treatment.

Key Words: IVIG-resistant Kawasaki disease, IVIG, MTX, steroid

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INTRODUCTION

Kawasaki disease is an acute febrile disease of unknown etiology that generally affects children younger than 5 years old. It is a systemic vasculitis that invades small and medium-sized arteries, particularly coronary arteries, and results in complications, such as myocarditis, pericarditis, and ischemic heart disease.

The infusion of intravenous immunoglobulin (IVIG) within 10 days of the onset of Kawasaki disease is known to reduce both the duration of fever[1,2] and the incidence of coronary artery disease, and thus together with aspirin are the standard treatment. However, 20% of children show persistent or recurrent fever despite IVIG, and progression of coronary artery aneurysm formation.[2,3] There is still no established method of treating patients unresponsive to IVIG treatment, which makes this topic the subject of much research.

We report the case of a patient, diagnosed with Kawasaki disease, who despite three courses of IVIG with steroid had recurrent fever and progressive coronary artery disease, but who finally responded to methotrexate (MTX).

CASE REPORT

Patient: 0 0 Ham, M/6

Chief Complaint: Fever for 5 days and a rash for 3 days

Present Illness: This 6-year old patient was hospitalized in another hospital for an initial complaint of fever of 5 days duration, bilateral conjunctivitis, a strawberry tongue, and a rash of

3 days. He was diagnosed with Kawasaki disease and was given IVIG, but his fever did not subside and his coronary artery disease progressed, which led to his transfer to our hospital.

Past and family history: The patient was born full-term NSVD with a birth weight of 3.0 kg and had no historay of illness or hospitalization. There was no related family history.

Physical exam: Upon admission, the patient was acutely ill-looking and showed general weakness. His blood pressure and pulse rate were stable and his initial body temperature was 38℃. He had bilateral conjunctivitis, his lips were red and dry, but he showed no neck stiffness. His lung sounds were clear and his heart beat was regular with a grade I systolic ejection murmur. His abdomen was soft and flat and there was no hepatosplenomegaly. He had desquamation of his hands and feet and complained of general myalgia. He showed no scrotal swelling but there was direct tenderness, which subsided when the fever subsided.

Laboratory data: The patient showed leukocytosis on day 5 of his illness and thrombocytosis on day 12. His white blood cell count was 24,380/mm^3 on day 25, his platelet count 1497k/mm^3; both these counts decreased slowly until day 70 of his illness. Initial erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were elevated at 66 mm/hr and 30 mg/dl respectively, and decreased to 7 and less than 0.1 on day 66. On day 103, his ESR was 30 and CRP 0.12. All blood, urine, and stool cultures taken on days 5 and 16 of his illness were negative. Rheumatoid factor (RF), antinuclear antibody (ANA), and anti-DNA antibody titers were performed on days 19 and 30 to exclude the possibility of rheumatoid disease, and were all negative. On day 16, routine chemical studies showed that total protein and albumin were 8.1 and 2.0 g/dL, and on day 31 aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were 234 and 213U/L; these levels subsequently decreased to normal levels. EB VCA IgM was weakly positive, and EB VCA IgG and EBNA were positive, showing reactivated infection (Table 1).

An echocardiogram performed on day 6 of his illness showed normal coronary arteries, whereas subsequent echocardiograms showed mild coronary artery dilatation on the 2nd week and minimal pericardial effusion on day 26. During the 2nd month of his illness the coronary artery aneurysm progressed with a right coronary artery diameter of 3.6 - 11 mm, and a left coronary artery diameter of 6 - 8 mm. After the fever subsided, there was no further progression of the coronary artery disease (Table 2).

On day 79 the echocardiogram showed massive bilateral coronary aneurysmal ectasia. The right coronary artery diameter was 3.6 - 11 mm and the left coronary artery diameter 6.0 mm. There was no definite intralumen thrombi, no pericardial effusion, no regional wall motion abnormality, and the ejection fraction was normal (Fig. 1). Heart MRI on day 104, showed a multifocal coronary aneurysm of the entire right coronary artery and proximal to the mid left anterior descending artery. Short axis cine images showed no definite wall motion abnormality of the left ventricle (Fig. 2), and EKGs were normal. Abdominal ultrasonograms showed a dilated gall bladder. An ultrasonogram was performed to evaluate the scrotal

Table 1. Change of Coronary Artery Diameter and Laboratory Finding

Onset (day)	6	14	23	31	69	79	104
	◀		Echocardiogram			▶	HeartMRI
RCA(mm)	Normal	Ectatic change	2.3 - 6.8	5 - 7.5	3.6 - 11	9 - 11	7.8
LCA(mm)	Normal	Normal	4.5 - 4.7	4.3	6	4 - 6	4.2
ESR(mm/hr)	66	100	70	46	7	28	30
CRP(mg/dl)	30	24	14	10	< 0.1	0.67	0.12
Platlet(/mm^2)	305 k	633 k	1497 k	961 k	572 k	522 k	472 k

RCA, right coronary artery; LCA, left coronary artery; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

Table 2. Clinical Course and Treatment

Onset	0 5	12	14	19	22	26	30	31	38	45	52	59	66	73
Fever	38'C^^^^^^^^^^^^^^^^^^^				^^^^^		^^		^^^					
	36.5'C	^^^				^^^^		^^^^^^^^	^^					
IVIG	2 g/kg	1 g/kg, 1 g/kg						400 mg/kg × 5 days, 2 times						
Dexa					0.3mg/kg			0.6 mg/kg	0.6 mg/kg		tapering			
MTX	10 mg/BSA, weekly							◆	◆	◆	◆	◆	◆	◆
Aspirin	100 mg/kg							5 mg/kg						

IVIG, intravenous immunoglobulin; Dexa, dexamethasone; MTX, methotrexate.

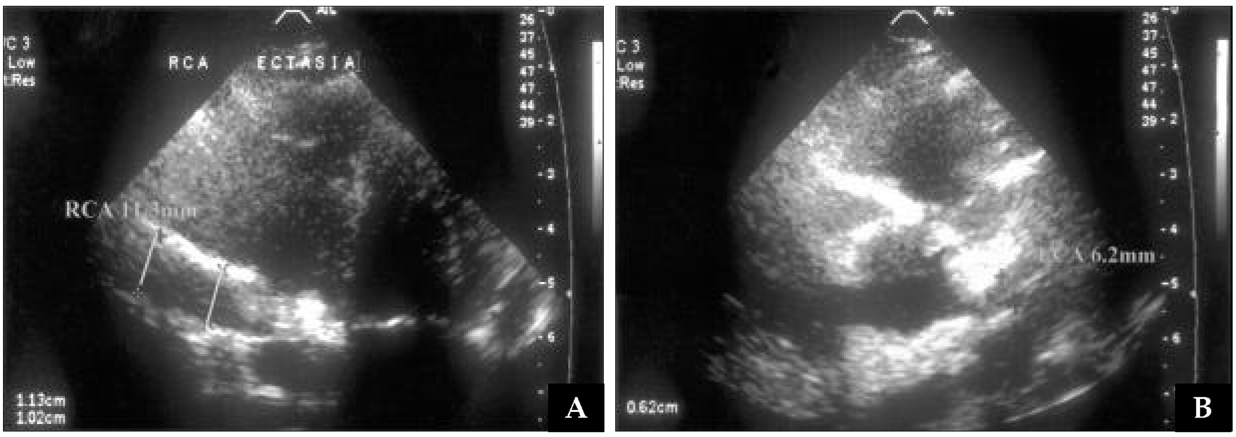

Fig. 1. Echocardiogram on day 79, showed massive bilateral coronary aneurysmal ectasia as a sequela of Kawasaki disease. The right coronary artery diameter was 3.6 - 11 mm (A), the left coronary artery diameter 6.0 mm (B).

tenderness, and revealed no torsion, but possible epididymitis.

Progress: Though IVIG was given to the patient on days 5, 12, and 14 of his illness at doses of 2 gm/kg, and 1 gm/kg, 1 gm/kg respectively, a fever of more than 380C persisted until day 19 of his illness, An echocardiogram on day 6 showed normal coronary arteries, but in the second week of illness, a follow-up echocardiogram showed right coronary artery dilatation progressing to coronary artery aneurysm. On day 19, dexamethasone (0.3 mg/kg for 3 days) was administered and his fever subsided. However, after discontinuing treatment, his fever recurred and dexamethasone was given again (0.3 mg/kg for 3 days) whereupon his fever subsided, but recurred when dexamethasone was again discontinued. On day 31, a fourth course of IVIG was given (400 mg/kg for 5 days) and the fever subsided. On day 36, the fever recurred whereupon IVIG (400 mg/kg for 5 days), dexamethasone (0.6 mg/kg for 10 days) and MTX (10 mg/BSA orally once a week) was given. The fever subsided from day 38 onwards. Dexamethasone was given for 10 days followed by prednisolone, which was then tapered and discontinued. The patient is currently taking aspirin (5 mg/kg) and renitec, and given MTX once a week orally.

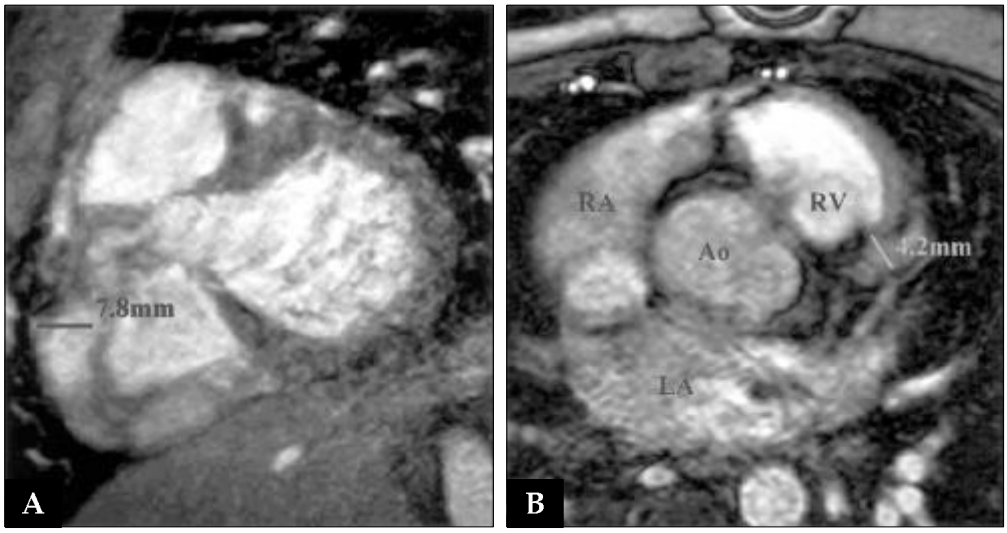

Fig. 2. Heart MRI on day 104, showed a multifocal coronary aneurysm on the entire right coronary artery (maximum: 7.8 mm)(A) proximal to the mid left anterior descending artery (maximum: 4.2 mm)(B).

DISCUSSION

Kawasaki disease is an acute febrile disease that was first described by Tomisaku Kawasaki in 1967. The immunologic and infectious mechanisms of Kawasaki disease are currently being proposed; the self-limiting nature, prevalent age, and regional and endemic nature of the disease supports the theory that it has an infectious basis. On the other hand, its involvement of arteries, similar to other immunologic diseases, supports immunologic basis.

The vasculitis in Kawasaki disease is brought about by an activated immune process, where by cytokines stimulate the production of antibodies against endothelial cells, causing immune complexes to be produced, which subsequently activate the complement system and the platelet system. This leads to the production of inflammatory intermediates and neutrophils activated by ANCA, which in turn results in the excretion of cytotoxic substances.[4] In addition, a mechansm in which cytotoxic cells directly attack endothelial cells infected by an as yet unknown agent is being proposed.[5]

The complications of this disease include myocarditis, pericarditis, and coronary artery aneurysm, and in cases where fever persists for more than ten days there is a higher risk coronary artery aneurysm formation.[6] The febrile period is believed to reflect proinflammatory cytokines increase, such as that of interleukin-1 (IL-1) and the severity of the vasculitis.[7] Furthermore, coronary artery aneurysm usually develops in 1 - 2 weeks and peaks in 4 - 8 weeks, resulting in possible sudden death; thus defervescence is the main goal during the acute period.

Since the first reports of Kawasaki disease, oral prednisolone and aspirin were the standard treatment; However, steroid use diminished after a study by Kato in 1979, which reported that among 17 patients who took oral prednisolone for 42 weeks, 65% (11 patients) developed coronary artery aneurysm[8]. Unfortunately, this report failed to stratify patients according to the risk factors of coronary aneurysm and provided no information on patient characteristics. It is also of note that 7 patients who received prednisolone and aspirin did not develop coronary disease.

After reports that IVIG reduces the incidence of coronary aneurysm from 20 - 25% to 2 - 4%, IVIG in combination with aspirin has been established as the standard treatment for Kawasaki disease.[2,9]

It has been proposed that IVIG in large doses acts directly on the blood vessel walls to suppress inflammatory reactions and activate the immune system. It inhibits the Fc portion of the immune complex and prevents the adhesion of platelets to

the vessel walls, preventing thrombosis and the formation of antibodies against an as yet unidentified antigen. Furthermore, the antiinflammatory effect of immunosuppression results in defervescence and reduced leukocytosis, reducing the acute reaction.[2,10]

However, despite IVIG infusion, 20% of cases show either persistence or recurrence of fever and the progression of coronary artery aneurysm, and this remains a subject of much interest and research. According to a study conducted by Nonaka et al. In which a comparison was made between children given IV steroids and children treated with low dose IVIG (300 mg/kg) for 3 days, the steroid-treated group showed a significantly reduced febrile period, but there was no difference in the incidence of disease.[11]

Another study reported that IVIG and oral steroids both significantly reduced the incidence of coronary artery aneurysm.[12,13] Wright et al. treated 4 patients unresponsive to a second course of IVIG with methylprednisolone (30 mg/kg) and reported improved clinical symptoms and the prevention of progression to coronary artery aneurysm.[14] Dahlem et al. reported a significant improvement in IVIG-resistant Kawasaki disease patients who developed complications such as pericarditis, pleuritis, and ascites, which did not respond to a repeated infusion of IVIG, but who showed a significant improvement within 48 hours on methylprednisolone.[15] Shinohara et al. reported that prednisolone treatment significantly reduced the febrile period and the development of coronary aneurysm.[16] Wallace et al. conducted a study in which 15 of 65 Kawasaki disease patients (23%) required re-treatment, and among these patients, 5 patients (8%) developed coronary artery aneurysm. Patients who despite 3 - 4 courses of IVIG infusion showed no improvement, were given methylprednisolone, which resulted in a dramatic improvement of symptoms. Two patients showed a recurrence of fever after ceasing steroid treatment, and thus cyclophosphamide was administered. After discharge, oral steroid was given together with cyclophosphamide, and both were slowly tapered.[17]

MTX was initially used as an anti-cancer drug, and since the mid-1950s it has been used for a variety of diseases, including systemic rheumatoid arthritis. The mechanism of low-dose MTX is unknown, but its action as a dihydrofolate reductase (DHFR) inhibitor, as an inhibitor of other folate-dependent enzymes, and as an immunosuppressant and anti-inflammatory agents are currently being investigated. It has been proposed that these combined roles serve as a mechanism for its action in rheumatoid diseases. The anti-inflammatory action of low-dose MTX has been proposed to reduce CRP and ESR, and to inhibit the production of leukotrienes (LT)B4.[18] Until now, there have been no reports upon the treatment of Kawasaki disease with MTX. We used MTX at a low dose expecting to achieve anti-inflammatory and immunosuppressive effects. As our report shows, MTX was effective in Kawasaki disease that had no response to IVIG and steroid therapy. We report here for the first time that MTX is a potential treatment for IVIG resistant Kawasaki disease. Further research on the use of MTX in IVIG resistant Kawasaki disease must be undertaken, and its benefits and potential side effects elucidated.

We report the case of a patient who visited another hospital with an initial complaint of fever lasting for 5 days and rash for 3 days, who was diagnosed as having Kawasaki disease and who despite treatment with IVIG, experienced fever recurrence and developed coronary artery aneurysm. After being transferred to our hospital, he was treated with MTX.

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