

Methylprednisolone pulse therapy for massive lymphadenopathy in a child with intravenous immunoglobulin-resistant Kawasaki disease

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Kawasaki disease (KD) is an acute febrile multi-system vasculitis of unknown etiology. The diagnosis is based on clinical features. We describe a case of intravenous immunoglobulins (IVIG)-resistant KD presenting with persistent fever and massive cervical lymphadenopathy associated with mild respiratory distress. The symptoms resolved after methylprednisolone pulse therapy. High-dose pulse steroid may be an alternative therapeutic option in KD which presents with possible life-threatening complications or failure to respond to high-dose IVIG infusion.

Key words: Drug pulse therapy, intravenous immunoglobulins, methylprednisolone, mucocutaneous lymph node syndrome

Kawasaki disease (KD), first described by Tomisaku Kawasaki in 1967, is an acute febrile multi-system vasculitis of unknown etiology that most commonly affects children under 5 years old [1]. The diagnosis is based on the presence of fever for at least 5 days in addition to 4 of the following 5 criteria: polymorphous skin rashes; bilateral non-purulent conjunctival injection; mucosal inflammation (injected pharynx, fissured lips, strawberry tongue); peripheral extremity changes (indurative edema of the palms and soles followed by desquamation); and unilateral cervical lymphadenopathy [1,2]. The presentation of KD with lymphadenopathy as the predominant manifestation is unusual [3,4]. The most serious complications are coronary artery lesions such as coronary artery ectasia or aneurysm formation. Current treatment for acute KD is a single high dose of intravenous immunoglobulins (IVIG) at 2 g/kg along with aspirin at 80 to 100 mg/kg/day [5]. Nonetheless, about 20% of patients may have persistent or recrudescence fever despite a single dose of IVIG and may need a second infusion [6]. For this condition, high-dose pulse steroid may be an alternative therapeutic option. We describe a case of IVIG-resistant KD in a

patient with persistent fever and massive cervical lymphadenopathy that was successfully treated with methylprednisolone (MP) pulse therapy.

Case Report

A previously healthy 2-year-old boy was admitted to our hospital due to spiking fever for 5 days. Physical examination revealed an ill-looking child who always maintained his neck in a fixed posture with restriction of movements. Mild respiratory distress was also noted. Vital signs included temperature 38.5°C, heart rate 141 beats/min, respiratory rate 40 beats/min, and blood pressure 104/50 mm Hg. He had bilateral conjunctivitis, red and dry lips, polymorphous skin rashes, as well as indurative edema of the palms and soles. Erythematous induration of bacillus Calmette-Guérin vaccination scar was also noted. The most remarkable sign was unilateral massive lymphadenopathy (Fig. 1). Breathing sounds were clear and heart sounds were regular without murmur. His abdomen was soft and flat and no hepatosplenomegaly was noted. No other abnormal findings were noted on examination.

Initial laboratory data included the following: a leukocyte count of 9600/mm³ with 77% neutrophils, 10% bands, 7% lymphocytes, and 6% monocytes; hemoglobin 11.3 g/dL; and a platelet count of 249,000 cells/mm³. The C-reactive protein level was 190.5 mg/L. Serum

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Fig. 1. The photo shows a 7 × 8 cm tender huge neck mass with erythematous cutaneous change.

biochemistry results were as follows: blood urea nitrogen and creatinine within normal limits; glutamate pyruvate transaminase 51 U/L, glutamate oxaloacetate transaminase 121 U/L, and albumin 2.4 g/100 mL. Culture of blood specimens obtained on admission was negative. Epstein-Barr virus capsid antigen immunoglobulin M was negative. Chest radiograph and electrocardiogram were both normal. The echocardiogram showed normal coronary arteries. Abdominal ultrasonogram revealed mild thickening of the gallbladder wall and minimal ascites.

After admission, a course of high-dose IVIG (2 g/kg) along with high-dose aspirin (80 mg/kg/day) was given. Over the next 48 h, the boy remained ill and the fever persisted. In addition, the size of the neck mass progressed rapidly to a diameter of 7 by 8 cm and was associated with respiratory distress. Computed tomography scan of the neck was arranged which revealed massive cervical lymphadenopathy extending into the retropharyngeal region and compressing the airway (Fig. 2, Fig. 3). Therefore a second dose of IVIG (2 g/kg) was given under the impression of resistance to IVIG treatment. However, no significant improvement resulted. The patient continued to exhibit

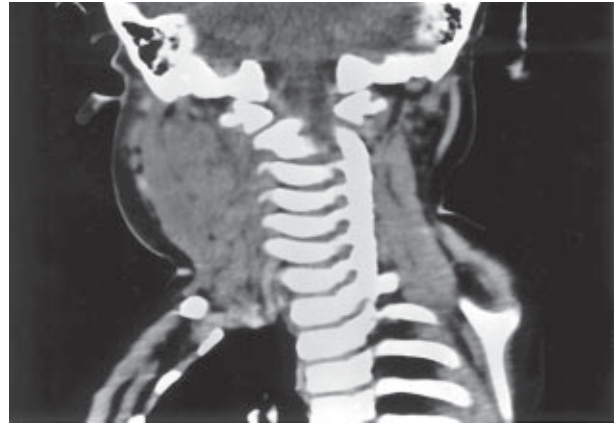


Fig. 2. Computed tomography scan reveals massive lymphadenopathy over the right neck area.

spiking fever with persistent lymphadenopathy. On day 6 of the illness, a follow-up echocardiogram showed coronary artery dilatation with the left coronary artery 3.5 mm and right coronary artery 3.2 mm in diameter. Due to progressive deterioration of the patient's condition, MP pulse therapy was given at a dose of 30 mg/kg/day for 3 days. After the first dose, a dramatic improvement in his condition occurred with prompt defervescence (Fig. 4). A rapid reduction in the size of cervical lymphadenopathy also occurred, and the absence of respiratory distress was noted upon completion of a 3-day course of MP. After the condition had stabilized, he was discharged with a prescription for low-dose aspirin (5 mg/kg/day). Follow-up echocardiogram at 12 weeks after the onset of the illness

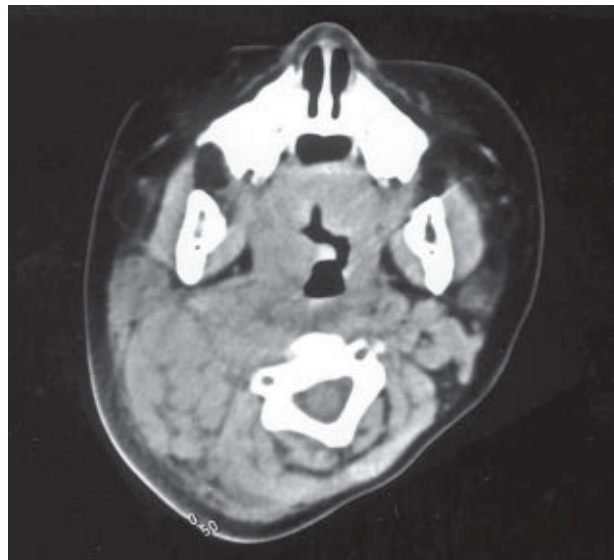


Fig. 3. Computed tomography scan reveals massive lymphadenopathy extending into the retropharyngeal region with airway compression.

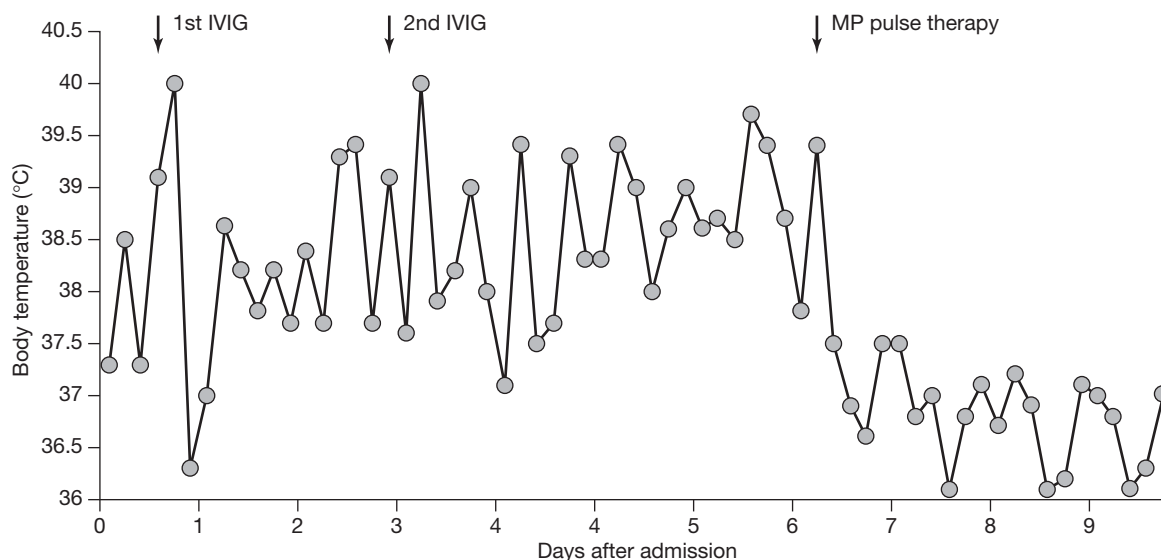


Fig. 4. Body temperature and treatment course during hospitalization in the patient with Kawasaki disease. IVIG = intravenous immunoglobulins; MP = methylprednisolone.

showed normal coronary arteries. He was still well after a follow-up of 1 year.

Discussion

The current recommended treatment for acute KD is a single high dose of IVIG 2 g/kg along with aspirin at 80 to 100 mg/kg/day [5]. The following mechanisms have been proposed to account for the immunomodulatory effects of IVIG in KD and other immune-mediated diseases: 1) blockade of Fc receptors on monocytes/macrophages; 2) induction of inhibitory Fc γ receptor IIB; 3) induction of anti-inflammatory cytokines; 4) inhibition of endothelial cell activation; 5) inhibition of complement-mediated damage; 6) neutralization of bacterial toxins or T cell superantigens; 7) neutralization of circulating autoantibodies by complementary antibodies; and 8) regulation of apoptosis [7,8]. However, the mechanisms of action of successful IVIG infusions are not yet completely understood.

There was a failure rate of about 20% with IVIG in the treatment of KD [6]. Reported risk factors for failure to respond to IVIG include low hemoglobin (<10 g/dL), high neutrophil count (>75%), high band count and low serum albumin [9]. Based on these risk factors, we were able to better predict that our patient would be more prone to a poor response to IVIG treatment.

Some reports have noted that retreatment of refractory KD with IVIG is effective in reducing fever [10-12]. However, our patient responded poorly to the second dose of IVIG and had prolonged fever for more

than 10 days. There are higher risks for development of coronary artery aneurysm formation when fever persists for more than 10 days [13]. Furthermore, the presentation of KD with lymphadenopathy as the predominant manifestation is unusual, and it rarely occurs to such a massive extent that it compresses the airway as in our patient [3,4]. There is still no well established method to treat KD patients in whom inflammation persists after the second dose of IVIG.

The role of steroids or other anti-inflammatory agents in the treatment of patients with refractory KD is still controversial. A possible role of corticosteroids in the treatment of the acute phase of KD had been suggested [14]. Some reports have suggested that MP pulse therapy may be an alternative therapeutic option for patients with IVIG-resistant KD. Wright et al treated 4 children with KD resistant to a second course of IVIG with MP (30 mg/kg, 1~3 doses). All 4 children apparently responded with normalization of symptoms, and none had significant progression of coronary artery abnormalities or adverse events [12]. Dahlem et al reported that a child with IVIG-resistant KD who developed a large pericardial effusion with symptoms suggesting cardiac tamponade showed significant improvement within 48 h after MP [15]. Wallace et al reported on the retreatment of 15 (23%) of 65 KD patients, among whom 5 had persistent disease with coronary aneurysms and/or coronary artery thrombosis. Four of these 5 patients were then treated with MP and 2 who were unable to tolerate discontinuation of MP without the symptoms of active KD reoccurring were

also treated with intravenous cyclophosphamide. There was no progression of coronary artery dilatation and no formation of new aneurysms once MP had been started [6]. Hashino et al reported a comparative study of additional IVIG (1 g/kg) and pulse steroid therapy in the retreatment of 35 (13.4%) of 262 KD patients who failed to respond to IVIG (2 g/kg) and aspirin (30 mg/kg/day), 17 of whom did not respond to the second dose of IVIG retreatment [16]. Nine of these 17 patients were treated with pulse steroid therapy and the others were treated with the third dose of IVIG (1 g/kg). There was no significant difference in the occurrence of coronary artery lesions between the 2 groups, but a difference was noted in the reduction of the duration of fever in the pulse steroid therapy group. However, transient dilatation of the coronary artery was observed during steroid pulse therapy, indicating the need for careful echocardiographic examination in patients receiving pulse steroid therapy [16]. Sundel et al conducted a randomized trial (n = 39) in which 18 KD patients received MP (30 mg/kg) with IVIG (2 g/kg) and aspirin (80~100 mg/kg/day), and the others received IVIG and aspirin alone. Treatment of acute KD with MP plus aspirin/IVIG, compared with aspirin/IVIG alone, resulted in faster resolution of fever, more rapid improvement in markers of inflammation, and a shorter length of hospitalization [17]. However, careful examination of this study reveals that the IVIG and aspirin group initially was somewhat more ill than the steroid group, with significantly lower serum albumin levels and somewhat higher C-reactive protein and alanine aminotransferase levels [18]. Thus, further assessment of the safety and efficacy of MP pulse therapy both in initial treatment and in IVIG-resistant KD patients is needed.

In summary, this case of IVIG-resistant KD with massive lymphadenopathy and complicated by respiratory distress dramatically resolved after MP treatment. This report may serve as a reminder that MP may be an alternative therapeutic option in KD with possible life-threatening complications or failure to respond to IVIG therapy.

References

1. Kawasaki T. Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children. *Allergy* 1967;16:178-222.
2. Burns JC, Kushner HI, Bastian JF, Shike H, Shimizu C, Matsubara T, et al. Kawasaki disease: a brief history. *Pediatrics* 2000;106:e27.
3. Burgner D, Festa M, Isaacs D. Delayed diagnosis of Kawasaki disease presenting with massive lymphadenopathy and airway obstruction. *BMJ* 1996;312:1471-2.
4. Shetty AK, Homsy O, Ward K, Gedalia A. Massive lymphadenopathy and airway obstruction in a child with Kawasaki disease: success with pulse steroid therapy. *J Rheumatol* 1998; 25:1215-7.
5. Dajani AS, Taubert KA, Gerber MA, Shulman ST, Ferrieri P, Freed M, et al. Diagnosis and therapy of Kawasaki disease in children. *Circulation* 1993;87:1776-80.
6. Wallace CA, French JW, Kahn SJ, Sherry DD. Initial intravenous gammaglobulin treatment failure in Kawasaki disease. *Pediatrics* 2000;105:e78.
7. Spellberg B. Mechanism of intravenous immune globulin therapy. *N Engl J Med* 1999;341:57-8.
8. Kazatchkine MD, Kaveri SV. Immunomodulation of auto-immune and inflammatory diseases with intravenous immune globulin. *N Engl J Med* 2001;345:747-55.
9. Durongpisitkul K, Soongswang J, Laohaprasitiporn D, Nana A, Prachuabmoh C, Kangkagate C. Immunoglobulin failure and retreatment in Kawasaki Disease. *Pediatr Cardiol* 2003; 24:145-8.
10. Sundel RP, Burns JC, Baker A, Beiser AS, Newburger JW. Gamma globulin re-treatment in Kawasaki disease. *J Pediatr* 1993;123:657-9.
11. Burns JC, Capparelli EV, Brown JA, Newburger JW, Glode MP. Intravenous gamma-globulin treatment and retreatment in Kawasaki disease. US/Canadian Kawasaki Syndrome Study Group. *Pediatr Infect Dis J* 1998;17:1144-8.
12. Wright DA, Newburger JW, Baker A, Sundel RP. Treatment of immune globulin-resistant Kawasaki disease with pulsed doses of corticosteroids. *J Pediatr* 1996;128:146-9.
13. Koren G, Lavi S, Rose V, Rowe R. Kawasaki disease: review of risk factors for coronary aneurysm. *J Pediatr* 1986;108:388-92.
14. Shinohara M, Sone K, Tomomasa T, Morikawa A. Corticosteroids in the treatment of the acute phase of Kawasaki disease. *J Pediatr* 1999;135:465-9.
15. Dahlem PG, von Rosentiel IA, Lam J, Kuijpers TW. Pulse methylprednisolone therapy for impending cardiac tamponade in immunoglobulin-resistant Kawasaki disease. *Int Care Med* 1999;25:1137-9.
16. Hashino K, Ishii M, Iemura M, Akagi T, Kato H. Re-treatment of immune globulin-resistant Kawasaki disease: a comparative study of additional immune globulin and steroid pulse therapy. *Pediatr Int* 2001;43:211-7.
17. Sundel RP, Baker AL, Fulton DR, Newburger JW. Corticosteroids in the initial treatment of Kawasaki disease: report of a randomized trial. *J Pediatr* 2003;142:611-6.
18. Shulman ST. Is there a role for corticosteroids in Kawasaki disease? *J Pediatr* 2003;142:601-3.