CASE REPORT

Steroid Pulse Therapy for Kawasaki Disease Complicated with Myocarditis

TOMOMI SATO, JUNPEI SOMURA AND YOSHIHIRO MARUO

From the Department of Pediatrics, Shiga University of Medical Science, Seta Tsukinowa-cho, Otsu, Shiga, Japan.

Correspondence to: Dr Tomomi Sato, Department of Pediatrics, Shiga University of Medical Science, Seta Tsukinowa-cho, Otsu, Shiga, Japan. ttflutedr@yahoo.co.jp
Received: August 25, 2015; Initial review: October 20, 2015; Accepted: August 02, 2016.

Background: The clinical management of intravenous immunoglobulin-resistant Kawasaki disease shock syndrome (KDSS) is obscure. **Case characteristics**: Three children presented with intravenous immunoglobulin-resistant KDSS complicated with myocarditis. **Outcome:** All cases were successfully managed with steroid pulse therapy. **Message:** Steroid pulse therapy is effective in immunoglobulin-resistant KDSS.

Keywords: *Corticosteroids, Gamma-globulins, Heart failure, Kawasaki syndrome.*

Kawasaki disease shock syndrome (KDSS) is a rare complication of Kawasaki disease (KD), which manifests as hemodynamic instability during the acute phase of KD [1]. KDSS is associated with serious morbidity and mortality risks, and diagnostic challenges, especially when it involves myocarditis, pericarditis, a coronary artery aneurysm, and aortic root dilatation [2-4]. The first-line treatment modality for KDSS and KD is high-dose intravenous immunoglobulin (IVIG) and high-dose aspirin. IVIG treatment may decrease the risk of developing coronary artery aneurysms from 25% to 3%; however, in cases refractory to IVIG, treatment modalities are obscure [4].

We report the successful management of three cases of KDSS that showed a good response to steroid pulse therapy, although intravenous immunoglobulin was ineffective in all cases.

CASE REPORT

Case 1: A 2-year-old boy was diagnosed with KD. IVIG therapy (2 g/kg) was initiated; however, on day 6, the patient developed KDSS for which dobutamine (3 µg/kg/min) was started. The patient was then transferred to our hospital, as his symptoms were not alleviated. On arrival, he demonstrated hepatosplenomegaly and generalized edema, although electrocardiogram was normal. On day 9, his heart failure worsened. Steroid pulse therapy was administered from days 10–12, resulting in improved cardiac function on day 11 and dobutamine was discontinued. Oral prednisolone (1.2 mg/kg/day) was initiated on day 13 and tapered over 2 months. On day 25, coronary artery dilatation was found (1, 7.8 mm; 6, 6.4 mm), and warfarin administration was initiated (***Web Fig.* 1**). Cardiac catheterization indicated that dilatation of the coronary arteries persisted (1, 8 mm; 6, 4 mm) 6 months later, but this was not evident 3 years later (1, 4.2 mm).

Case 2: A 7-year-old girl diagnosed with KD was started on IVIG (2 g/kg/day) and oral aspirin (30 mg/kg/day) treatment. On day 6, she developed respiratory difficulty, hypotension (62/34 mmHg), and cardiac failure. Dilatation of the carotid artery was noted, and she was diagnosed with cardiogenic shock. Thus, dopamine (3µg/kg/min) and dobutamine (5µg/kg/min) administration were initiated (***Fig.* 1**). On day 7, her high fever persisted, despite an additional dose of IVIG (2 g/kg). On day 9, she was referred to our hospital. On admission, she received dopamine (5µg/kg/min) and dobutamine (5 µg/kg/min), and physical examination revealed: temperature, 39.5°C blood pressure 101/43 mmHg; pulse rate 100 beats/min respiratory rate 60 min; and oxygen saturation 95% (room air). Blood test results indicated leukocytosis (29,600/µL), elevated C-reactive protein (26.37 mg/dL), liver enzymes, and brain natriuretic peptide; and hypoalbuminemia. Echocardio-graphy showed hypo-kinetic cardiac wall motion with an ejection fraction (EF) of 44.0%. Mild dilatation of the coronary arteries was observed (1, 3.3 mm; 5, 3.7 mm). Pulse therapy with methylprednisolone (30 mg/kg/day, 3 days) was initiated. On day 10, the patient's fever decreased, and her EF improved to 66.0%. On day 11, catecholamine infusion was discontinued. On day 12, oral prednisolone (1.2 mg/day) was initiated and tapered over 3 weeks. Her subsequent clinical course did not demonstrate coronary artery aneurysm formation or impaired cardiac function (***Web Fig.* 1**).

Case 3: A 5-year-old boy presented with heart failure, for which dopamine (5 µg/kg/min) and dobutamine (5µg/kg/

min) administration were initiated (***Web Fig.* 1**). Since the symptoms were not alleviated, he was referred to our hospital where KD was diagnosed. Echocardiography showed an increased brightness of the coronary arteries and mild dilatation of the coronary arteries (1, 2.0 mm; 5, 3.0 mm). IVIG administration (2 g/kg) was initiated; however, the child continued to have high fever and cardiac failure. Plasmapheresis was started on day 9, but the child did not improve. On day 10, methylprednisolone pulse therapy (30 mg/kg/day, 3 days) was initiated. The child's fever decreased the following day, and his cardiac function improved. On day 12, catecholamine infusion was discontinued. On day 13, oral prednisolone (1.5 mg/kg/day) was initiated and tapered over 1 year. He was discharged on day 27 without coronary artery dilatation or the presence of a coronary artery aneurysm.

DISCUSSION

KDSS is a rare condition that manifests with clinical features similar to those seen in cases of KD with systolic hypotension or poor perfusion [3,5,6]. In cases of KDSS resistant to IVIG, a treatment approach has not yet been established. In a study, IVIG-resistant KDSS was defined as persistent/recrudescent fever and no improvement of cardiac failure symptoms at least 48 hours after completing the first IVIG infusion [7]. Lin, *et al*. [8] reported a 1.2% incidence of KDSS in the KD population, and in another study, the incidence of KDSS was about 5% of all KD cases. It was also reported that 60% of patients with KDSS develop IVIG resistance, whereas only 12% of patients with KD develop IVIG resistance [3].

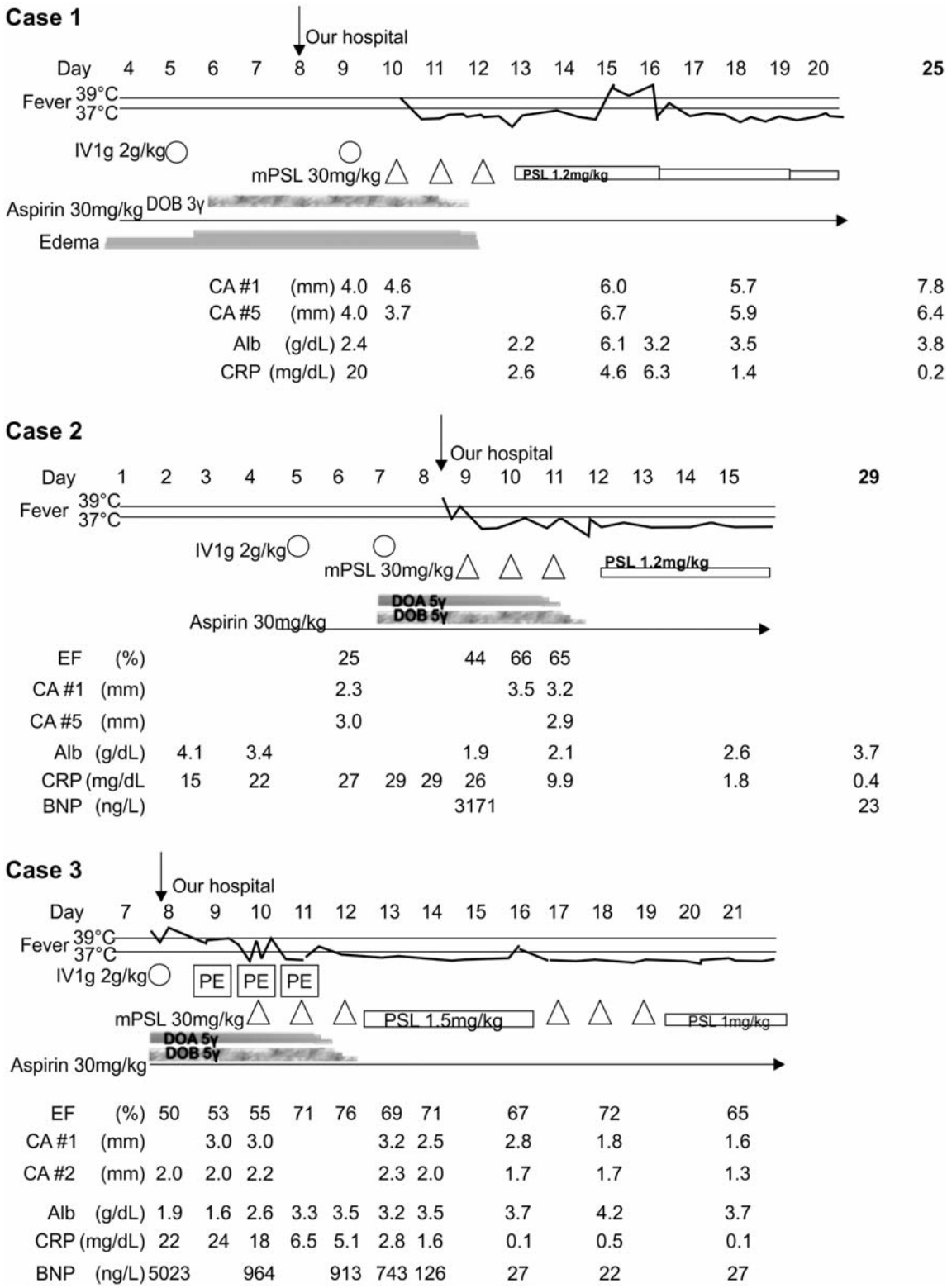
The reported children displayed persistent high fever and cardiac failure, despite IVIG treatment and in the absence of any concurrent infection. The first case developed symptoms of KDSS on the sixth day after diagnosis, whereas in the second and third case, KDSS was confirmed after 9 days. The diagnosis of KD was made within 5 days in all cases, and IVIG was initiated in all cases. In case 1, dobutamine was initiated to resolve cardiogenic shock, as it directly stimulates â1 receptors of the sympathetic nervous system. However, it was ineffective. In second case, dopamine (3 µg/kg/min) and dobutamine (5µg/kg/min) were administered, and even an additional dose of gamma globulin (2 g/kg) was given; however, the patient's condition did not improve. In the third case, globulin and plasmapheresis were ineffective. In all three cases, fever and an inflammatory response continued to increase with the advent of heart failure accompanied with myocarditis. Since the heart failure responded well to steroid pulse therapy, we were able to stop catecholamine treatment soon. These cases indicate stronger systemic inflammation in KDSS, which requires a powerful immunosuppressive therapy.

Glucocorticoids are widely used as anti-inflammatory and immunosuppressive therapies for several conditions, although the use of corticosteroids for myocarditis is controversial. The reported cases are important, as they support growing evidence regarding the suitability of using glucocorticoids in such cases [9,10]. Interestingly, Aggarwal, *et al*. [10] recently reported methylprednisolone as rescue therapy in children with KD who had symptomatic congestive cardiac failure during the acute stage of the disease.

In conclusion, steroid pulse therapy can be an effective treatment modality in cases of IVIG-refractory KDSS that are complicated with myocarditis. More large-scale prospective studies are needed to fully determine the benefit of steroid pulse therapy in IVIG-refractory KDSS.

REFERENCES

1. Chen PS, Chi H, Huang FY, Peng CC, Chen MR, Chiu NC. Clinical manifestations of Kawasaki disease shock syndrome: a case-control study. J Microbiol Immunol Infect. 2015;48:43-50.
2. Dahdah N. Not just coronary arteritis, Kawasaki disease is a myocarditis, too. J Am Coll Cardiol. 2010;55:1507-7.
3. Gámez-González L, Murata C, Muñoz-Ramírez M, Yamazaki-Nakashimada M. Clinical manifestations associated with Kawasaki disease shock syndrome in Mexican children. Eur J Pediatr. 2013;172:337-42.
4. Kanegaye JT, Wilder MS, Molkara D, Frazer JR, Pancheri J, Tremoulet AH, *et al*. Recognition of a Kawasaki disease shock syndrome. Pediatrics. 2009;123:e783-9.
5. Huang SK, Lin MT, Chen HC, Huang SC, Wu MH. Epidemiology of Kawasaki disease: prevalence from national database and future trends projection by system dynamics modeling. J Pediatr. 2013;163:126-131.e121.
6. Nakamura Y, Yashiro M, Uehara R, Oki I, Watanabe M, Yanagawa H. Epidemiologic features of Kawasaki disease in Japan: results from the nationwide survey in 2005-2006. J Epidemiol. 2008;18:167-72.
7. Tremoulet AH, Best BM, Song S, Wang S, Corinaldesi E, Eichenfield JR, *et al*. Resistance to intravenous immunoglobulin in children with Kawasaki disease. J Pediatr. 2008;153:117-21.
8. Lin MT, Fu CM, Huang SK, Huang SC, Wu MH. Population-based study of Kawasaki disease shock syndrome in Taiwan. Pediatr Infect Dis J. 2013;32:1384-6.
9. Tse SML, Silverman ED, McCrindle BW, Yeung RSM. Early treatment with intravenous immunoglobulin in patients with Kawasaki disease J Pediatr. 2002;140:450-5.
10. Aggarwal P, Suri D, Narula N, Manojkumar R, Singh S. Symptomatic myocarditis in Kawasaki disease. Indian J Pediatr. 2012;79:813-4.



IV: intravenous, mPSL: methylprednisolone, PSL: prednisolone, DOB, dobutamine, CA: coronary artery, Alb, albumin, CRP: C-reactive protein, EF: ejection fraction, BNP: brain natriuretic peptide, PE: plasma exchange, DOA: dopamine.

***Web Fig.* 1** *Clinical course of the three cases of Kawasaki disease shock syndrome (KDSS).*