

รายงานผู้ป่วยโรคคาวาซากิที่ไม่ตอบสนองต่อการรักษามาตรฐาน  
(refractory Kawasaki disease) และมีการป้องกันของหลอดเลือดโคโรนารี  
ซึ่งตอบสนองต่อยา infliximab

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**บทคัดย่อ**

รายงานผู้ป่วยเด็กชายอายุ 1 ปี 11 เดือน ได้รับการวินิจฉัยว่าเป็นคาวาซากิ มีอาการไข้สูง ท้องเสีย ตาแดง ปากแดง ผื่น ต่อมน้ำเหลืองบริเวณคอด้านขวาอักเสบ มือและเท้าบวม พบการป้องกันของหลอดเลือดโคโรนารี 2 เส้น อาการของผู้ป่วยไม่ตอบสนองต่อการรักษาด้วยยา intravenous immunoglobulin (IVIG) 3 ครั้ง และ pulses methylprednisolone 3 ครั้ง แต่ตอบสนองดีโดยอาการไข้ ท้องเสีย และปากแดงหายไป ใน 24 ชั่วโมงหลังได้รับการรักษาด้วยยา infliximab 1 ครั้ง ซึ่งเป็น monoclonal antibody ต่อ tumor necrosis factor alpha

**คำสำคัญ:** โรคคาวาซากิ โรคคาวาซากิที่ไม่ตอบสนองต่อการรักษามาตรฐาน ยาอินฟลิซิแมบ การป้องกันของหลอดเลือดโคโรนารี

**ผู้พิมพ์ประสานงาน:**

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# A case report of refractory Kawasaki disease with coronary artery aneurysm responding to infliximab

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## Abstract

This case report describes a 1 year 11 month-old boy with refractory Kawasaki disease. He presented with prolong high grade fever, diarrhea, red eyes, dry cracked lips, rash, left lateral neck mass, hands and feet swelling and two coronary artery aneurysms. Treatment with three doses of intravenous immunoglobulin and three pulses of methylprednisolone were not responded. Finally, the patient was responsive to a single dose of infliximab, a monoclonal antibody against tumor necrosis factor alpha.

**Keywords:** Kawasaki disease, refractory Kawasaki disease, infliximab, coronary artery aneurysm

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## **A case report of refractory Kawasaki disease with coronary artery aneurysm responding to infliximab**

A 1 year 11 month-old boy presented with 9 days history of high grade fever, red eyes, dry and cracked lips, rash, left lateral neck mass, hands and feet swelling. He also had a history of reduced oral intake and watery diarrhea. Before coming to our hospital, he had been diagnosed as lymphadenitis on fever day 1 and treated with cefotaxime and amikacin. On fever day 2 the diagnosis as Kawasaki disease (KD) was made from clinical. He was treated with intravenous immunoglobulin (IVIG) 2 g/kg/dose and aspirin 90 mg/kg/day along with the antibiotics by a pediatrician at a community hospital. Without any improvement in signs and symptoms, the fever was high grade, on fever day 5, he was treated with the second dose of 2 g/kg IVIG. On fever day 7, no clinical improvement occurred except rash after two doses of IVIG treatment. The follow-up laboratory results on the seventh hospital day were as follow: hemoglobin 8.26 g/dL, WBC 21,000/ $\mu$ L (polymorphonuclear leukocytes 80%; lymphocytes 13%; monocytes 5%; eosinophil 2%), platelets  $334 \times 10^3$ / $\mu$ L, sodium 142 mEq/L, and the level of liver enzymes were increased; aspartate aminotransferase (AST) 172 U/L, alanine aminotransferase (ALT) 161 U/L, total bilirubin 0.6 mg/dL, direct bilirubin 0 mg/dL, the total protein/albumin was 7.2/2.5 mg/dL. Chest radiography showed interstitial

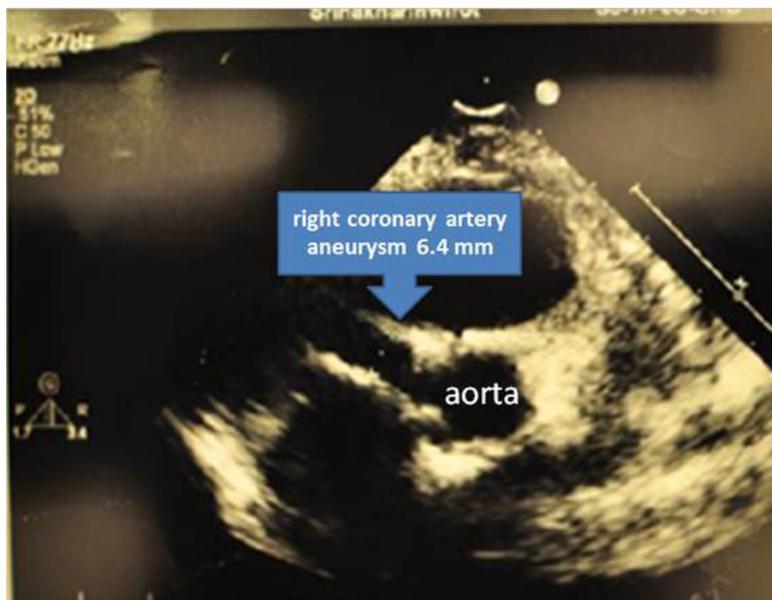
infiltration at right middle lung. The patient was given meropenem instead of previous antibiotics and pack red cell infusion.

On fever day 9, he was referred to our hospital with the problem of refractory Kawasaki disease. On examination, he had an irritable look, dry cracking lips, strawberry tongue and edema of the hands and feet. An erythematous, maculopapular rash on the face and limbs was observed. Breathing sounds were clear without crackles, and no cardiac murmur was audible. No evidence of cervical lymphadenopathy or conjunctival injection was noticed. He was febrile with a temperature of 39°C. His blood pressure was 102/60 mmHg. With this history and presentation, the initial impression was refractory Kawasaki disease. His baseline laboratory work up was sent. Abnormal laboratory findings included a low hemoglobin (9.5 g/dL), a low hematocrit (28%), raised white cell count (23,970/ $\mu$ L), with a predominance of polymorphonuclear leukocytes (71.4%) and thrombocytosis (platelet count of  $681 \times 10^3$ / $\mu$ L).

C-reactive protein (CRP) level was elevated to 14.5 mg/dL and Erythrocyte Sedimentation Rate (ESR) was raised (140 mm/hr). Level of liver enzymes were similar to previous study; AST 194 U/L, ALT 150 U/L, total bilirubin 0.58 mg/dL, direct bilirubin 0.29 mg/dL, the total protein/albumin was 7.2/2.6 mg/dL. The rest of the work-up including electrolyte, urine examination, renal function workup were within the normal range.

A chest radiography was unremarkable. In addition, his blood cultures showed no growth. An echocardiogram was performed which showed a normal left coronary artery

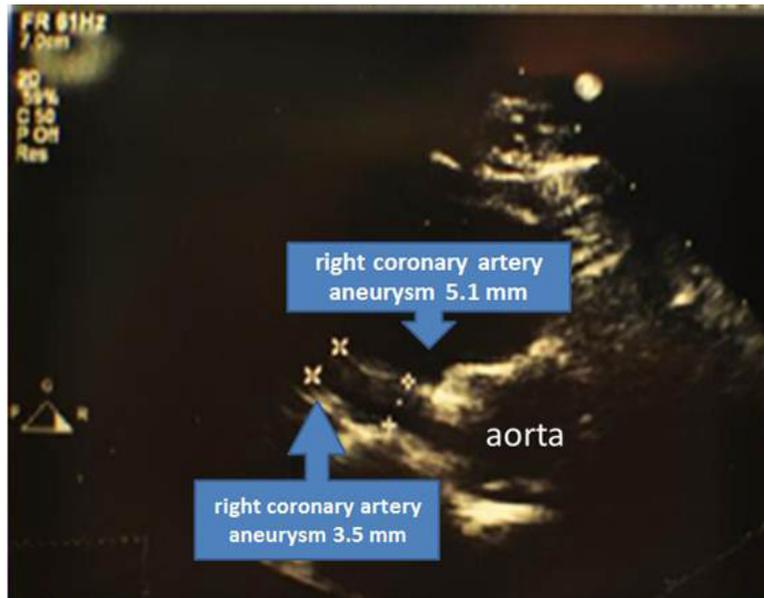
and right coronary artery aneurysm 6.4 mm (+12.52 SD), good left ventricular contraction (ejection fraction 62%) with mild mitral valve regurgitation (Figure 1).



**Figure 1:** Echocardiography. After second treatment of intravenous immunoglobulin the patient developed right coronary artery aneurysm.

He was given pulse methylprednisolone for 3 days and high dose aspirin (80 mg/kg/day). On fever day 13, the fever subsided and his symptoms slowly resolved but still had red lips, strawberry tongue and diarrhea. A repeat echocardiogram showing slightly improvement of right coronary artery aneurysm (5 mm, +8.78 SD) and a normal diameter of the left main coronary artery 2.2 mm, left anterior descending coronary artery (1.6 mm), left circumflex artery (1.6 mm).

On fever day 16, fever reappeared. He still had Kawasaki features fissured lips, and strawberry tongue and diarrhea. He revealed periungual peeling of fingers. His follow-up laboratory findings showed slightly improvement with a CRP of 3.8 mg/dl, ESR of 128 mm/hr and thrombocytosis platelets of  $924 \times 10^3/\mu\text{L}$ . Echocardiogram (Figure 2) showed two aneurysms of the right coronary artery (5.1 mm, +9.05 SD and 3.5 mm, +5.49 SD) and normal left coronary artery. He was given the third dose of IVIG (2 g/kg), aspirin (80 mg/kg/day) and clopidogrel (1 mg/kg/day).



**Figure 2:** Echocardiography. On fever day 16, after second courses of intravenous immunoglobulin and pulse methylprednisolone for 3 days, the patient developed two right coronary artery aneurysms.

After the fever day 18, he still had mild temperature elevation and diarrhea. Anti-nuclear antibody, Rheumatoid Factor, perinuclear-antineutrophil cytoplasmic antibody (p-ANCA) and cytoplasmic-ANCA (c-ANCA) were also sent which came back to be normal. A whole aorta magnetic resonance angiography (MRA) was also done; renal and mesenteric arteries were unremarkable. A diagnosis of polyarteritis nodosa was ruled out.

He was treated with infliximab (5 mg/kg/dose), aspirin (80 mg/kg/day) and clopidogrel (1 mg/kg/day) on fever day 29. The following day, the fever subsided and his symptoms of diarrhea, fissured lips and strawberry tongue resolved. Two years after

being discharged, the patient remained asymptomatic. Nevertheless, patient was continued on aspirin due to coronary artery lesion (CAL). Thereafter the CAL progressively improved and follow-up coronary MRA 3 years after onset of KD revealed completely resolution of his coronary aneurysm.

### Discussion

The etiology of KD is unclear. A typical case of KD can be diagnosed by the clinical criteria which are the presence of high fever lasting for 5 or more days, combined with at least four of the five following physical findings, bilateral bulbar conjunctival injection, oral mucous membrane changes, edema and desquamation of the peripheral

extremities, polymorphous rash and cervical lymphadenopathy (>1.5 cm in diameter) and exclusion of other illnesses.<sup>1</sup> Standard treatment of Kawasaki disease includes aspirin in combination with a single infusion of high dose IVIG (2 g/kg) and aims to reduce inflammation of the vascular beds and prevent cardiac complications.<sup>1</sup>

Our patient was administered the 2 doses of IVIG (on fever day 2 and day 5) and high dose aspirin prior to admission to our hospital. His clinical presentation and laboratory parameters include echocardiographic data showed aneurysm of coronary artery supported ongoing inflammation. Approximately 10-15% of the patients with KD have a persistent or recurrent fever after initial treatment.<sup>2-3</sup> Pulse methylprednisolone was administered in this case to control the symptoms after two doses of refractory IVIG treatment. Studies support the use of pulsed-dose methylprednisolone, 30 mg/kg/day administered intravenous daily for one to three days, in patients who fail to respond to IVIG therapy.<sup>4-7</sup> After failure to responding to 2 doses of IVIG and three pulsed methylprednisolone, we gave a third IVIG infusion on fever day 16 because immunosuppressive agent such as a monoclonal antibody against tumor necrosis factor alpha (TNF- $\alpha$ ) was not available. Although no efficacy data exist today to support administering a third dose of IVIG therapy, some reports suggest that retreatment with IVIG should be considered

if there is no response to two standard doses of IVIG treatment.<sup>8-9</sup>

Despite the infusion of the additional third dose IVIG, the fever and other KD features persisted. After a diagnosis of polyarteritis nodosa was ruled out and infliximab had been ordered to the hospital, we started a rescue therapy with IV infliximab 5 mg/kg single dose. Elevated level of TNF- $\alpha$  plasma concentrations and soluble TNF receptor concentrations are a characteristic of acute KD and associated with coronary artery aneurysms.<sup>10</sup> Thus using of infliximab in cases of refractory KD leading to a decline in fever and inflammatory activity and to a regression of coronary abnormalities.<sup>11-13</sup> Even though there were no reports of serious infections or malignancy from potent and potentially prolonged immunosuppressive effect of infliximab, it should be considered when treating children with this type of medication.

Due to our patient's severe presentation even an early diagnosis and timely starting of IVIG therapy was ineffective in preventing coronary artery aneurysms. According to scoring and new recommendations for additional therapies in updated the American Heart Association regarding the diagnosis and management of Kawasaki disease 2017, in order to identify the patients at high risk for unresponsiveness to IVIG therapy, this patient may benefit from primary adjunctive therapy by administration of a long course of corticosteroids (until

afebrile and tapering over 2-3 weeks) together with IVIG 2 g/kg and ASA.<sup>14</sup> However, there are no studies to prove accuracy of currently risk prediction models from Japanese study groups in predicting response to initial treatment with IVIG in Thai patients, which is likely that genetic factors play a role in the response and resistance to IVIG.<sup>2,14-16</sup> Further prospective study is necessary to developed predictive models for use in Thailand and to determine the optimal adjunctive therapies for patients with high risk for unresponsive to IVIG therapy and refractory KD.

## Conclusion

We have presented a case of refractory KD with severity of clinical presentation and early development of coronary artery aneurysms which response to infliximab after treated with three doses of IVIG and various pulses of methylprednisolone. Infliximab could be the option for resistant of KD especially after second regimen of IVIG and pulses methylprednisolone.

## Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

**Table 1:** Laboratory findings of the patient

Day	Hemoglobin (g/dL)	Platelets (/mm <sup>3</sup> )	White blood cell (/mm <sup>3</sup> )	Neutrophils (%)	C-Reactive protein (mg/dL)	Albumin (g/dL)	Sodium (mMoL/L)
2	12.0	262,000	17,800	84			140
7	8.3	334,000	21,000	80		2.5	142
9	9.5	681,000	23,970	71	14.5	2.6	136
13	10.8	880,000	26,770	68	6.9	2.9	137
16	9.6	924,000	26,490	54	3.8		
18	8.7	816,000	12,970	46	2.0	2.7	
23	9.9	568,000	14,580	50	0.1	3.6	
32	11.4	365,000	6,440	25	0.02		

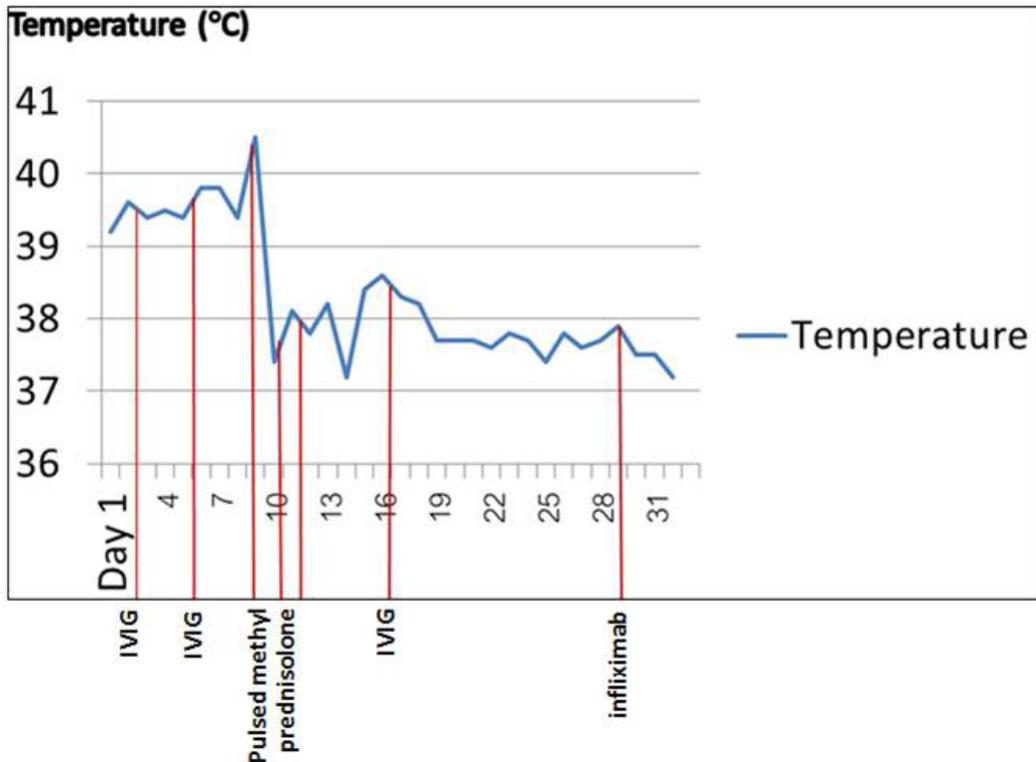


Figure 3: Graph representing the fever of the patient.

### References

1. Newburger JW, Takahashi M, Gerber MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. *Pediatrics* 2004;114(6):1708-33.
2. Egami K, Muta H, Ishii M, et al. Prediction of resistance to intravenous immunoglobulin treatment in patients with Kawasaki disease. *J Pediatr* 2006;149(2):237-40.
3. Uehara R, Belay ED, Maddox RA, et al. Analysis of potential risk factors associated with nonresponse to initial intravenous immunoglobulin treatment among Kawasaki disease patients in Japan. *Pediatr Infect Dis J* 2008;27(2):155-60.
4. Wright DA, Newburger JW, Baker A, et al. Treatment of immune globulin-resistant Kawasaki disease with pulsed doses of corticosteroids. *J Pediatr* 1996;128(1):146-9.
5. Raman V, Kim J, Sharkey A, et al. Response of refractory Kawasaki disease to pulse steroid and cyclosporin A therapy. *Pediatr Infect Dis J* 2001;20(6):635-7.

6. Hung JJ, Chiu CH. Pulse methylprednisolone therapy in the treatment of immune globulin-resistant Kawasaki disease: case report and review of the literature. *Ann Trop Paediatr* 2004; 24(1):89-93.
7. Lang BA, Yeung RS, Oen KG, et al. Corticosteroid treatment of refractory Kawasaki disease. *J Rheumatol* 2006; 33(4):803-9.
8. Kim JY, Kim HJ. A Case of Kawasaki Disease with Coronary Aneurysm Responding to the 4th IVIG Treatment. *Case Rep Cardiol* 2014;2014:821812.
9. Wallace CA, French JW, Kahn SJ, et al. Initial intravenous gammaglobulin treatment failure in Kawasaki disease. *Pediatrics* 2000;105(6):E78.
10. Levin M, Burgner D. Treatment of Kawasaki disease with anti-TNF antibodies. *Lancet* 2014;383(9930):1700-3.
11. Burns JC, Best BM, Mejias A, et al. Infliximab treatment of intravenous immunoglobulin-resistant Kawasaki disease. *J Pediatr* 2008;153(6):833-8.
12. Oishi T, Fujieda M, Shiraishi T, et al. Infliximab treatment for refractory Kawasaki disease with coronary artery aneurysm. *Circ J* 2008;72(5):850-2.
13. Son MB, Gauvreau K, Burns JC, et al. Infliximab for intravenous immunoglobulin resistance in Kawasaki disease: A retrospective study. *J Pediatr* 2011;158(4):644-9.
14. McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. *Circulation* 2017;135(17):e927-99.
15. Kobayashi T, Inoue Y, Takeuchi K, et al. Prediction of intravenous immunoglobulin unresponsiveness in patients with Kawasaki disease. *Circulation* 2006;113(22):2606-12.
16. Sano T, Kurotobi S, Matsuzaki K, et al. Prediction of non-responsiveness to standard high-dose gamma-globulin therapy in patients with acute Kawasaki disease before starting initial treatment. *Eur J Pediatr* 2007;166(2):131-7.