

A case report of refractory kawasaki disease

Nga Shih Hang, MRCPCH¹, Roshan Singh, MBBS²

¹Department of Paediatrics, Hospital Seri Manjung, Perak, Malaysia, ²Department of Paediatrics, Hospital Sultanah Bahiyah, Kedah, Malaysia

SUMMARY

Kawasaki disease is an autoimmune disease that commonly affects children below the age of 5 years. It is a vasculitic disease of unknown aetiology effecting the skin, eyes, lymph nodes and mucosal layer. Intravenous Immunoglobulin (IVIG) and aspirin therapy are the mainstay treatment however a number of cases have been shown to be refractory to this treatment. Evidence regarding approach and treatment for such cases is limited. This case report is to share our experience in the management of Refractory Kawasaki disease at a district level.

INTRODUCTION

Tomisaku Kawasaki first described a case of Kawasaki disease in January 1961 and published it in 1967.

The diagnosis of Kawasaki disease has always been a clinical diagnosis that fulfil the following five criteria;

- 1) Fever lasting at least for 5 days with at least 4 out of 5 of the following;
- 2) Bilateral non-purulent conjunctivitis
- 3) Mucosal changes of the oropharynx
- 4) Changes in the extremities (oedema and/or erythema of the hands or feet, desquamation, beginning periungually)
- 5) Rash (usually truncal) polymorphous but non-vesicular
- 6) Cervical lymphadenopathy

Kawasaki disease is vasculitic disease with a high predilection for the coronary arteries along with a number of immunoregulatory changes which include deficiency of circulating CD8+ suppressor/cytotoxic T cells, an abundance of circulating B cells spontaneously-producing immunoglobulins and circulating, activated monocytes.

Below we present a case report of Refractory Kawasaki disease of a 1 year 3-month male that presented to us in Hospital Seri Manjung.

CASE REPORT

A 1 year 3 months boy presented with history of fever for three days associated with cough, runny nose and rash for 1 day. He was prescribed erythromycin ethyl succinate by a general practitioner of which he developed rashes. Thus, given antihistamine for the reaction and the antibiotic was changed to intravenous crystalline penicillin.

However, he remained febrile despite on antibiotics. Initial CBC showed a TWBC of 11.1, Hb of 11.2 and platelet of 276, BU 4.5, Sodium 134, TP 63, albumin 28, AST 95, ALP 212 and ALT 216.

A day after admission he developed bilateral non-purulent conjunctivitis and cervical lymphadenopathy. A repeat blood investigation resulted in, TWBC 8.1, Hb 11.0, platelet of 261, BU 2.1, sodium 133, TP 62, albumin 26, AST 47, ALP 195, ALT 172. Blood work up showed a raised ESR with a value of 31mmHr. With the new signs developing, the diagnosis of Kawasaki Disease was made, at day-5 of illness.

Ultrasound Hepatobiliary system showed liver parenchymal disease with hydrops of the gall bladder.

ECG was normal, and a bedside ECHO showed increased in the left and right coronary artery measurement, more than the 95th centile.

He was prescribed IVIG 2g/kg given over 10 hours and aspirin 30mg/kg/day in four divided doses. After completing the IVIG we noted the temperature did not settle and a second dose of IVIG was decided with the same dose 2g/kg, about 24 hours after the first dose.

After completion of the second dose of IVIG, he remained febrile with temperatures of 40-degree celcius. The bloods were repeated, TWBC 25.8, Hb 8.3, platelet 484, BU 2.1, 137, TP 70, albumin 17, AST 21, ALP 129, ALT 39 and ESR>140. CRP was done and showed a positive result. He was started on broad-spectrum antibiotic (Ceftriaxone) intravenously. The diagnosis of refractory Kawasaki disease was made in view of the increasing ESR and platelet counts.

We started the child on high dose methylprednisolone 30mg/kg for a period of three days after discussion with paediatric cardiologist.

The temperature abated after the 2nd dose of the methylprednisolone. We completed a total of three days of methylprednisolone as planned. Patient was discharge after 48 hours of being afebrile, post completion of methylprednisolone.

In Table I it can be observed the serial laboratory workup that guided our team as well as aided us in the viewing of the effectiveness of the treatment.

Table I: Summary of Investigations

	25/8/15	26/8/15	31/8/15 9 (1st Dose IVIG)	1/9/15	11/9/15	28/9/15	12/10/15
White Blood Count (4000 – 11000 uL)	11.1	8.1	25.8	27.5	15.9	9.3	9.2
Hemoglobin (12.3 -15.5 g/dL)	11.2	11.0	8.3	8.2	8.2	10.5	11.1
Hematocrit (37-47%)	31.1	30.6	23.9	23.6	24.6	32.5	32.7
Platelet (150000-400000 uL)	276	261	484	598	701	795	511
Erythrocyte Sedimentation Rate (0-15mm/hour)		31	>140		>140	>140	39

A repeated ECHO two weeks after discharge and resulted in both left and right coronary dilation were static. The patient was continued on Tab Aspirin 30mg/kg/day for another two more weeks after which we repeated the ESR. The progression of the disease was monitored by serial ESR readings. He was then referred to a paediatric cardiologist for further consultation. His aspirin dose was reduced to antiplatelet dose i.e., 5mg/kg on the 12/10/2015 when the ESR was 39mm/hr, almost 45 days after the diagnosis.

DISCUSSION

As presented in the case above, the patient fulfilled the criteria for Kawasaki disease. Aspirin and IVIG were given as per recommended by multiple protocols. However, after more than 36 hours of completion of the second dose of IVIG the patient continued having temperature spikes. A retrospective study done in Japan in 2003-2004 noted that patient who didn't respond to IVIG was due to:³

- Initial treatment at or before the 5th day of the illness
- Recurrent episodes of Kawasaki disease
- Male sex

In addition to the above criteria there are certain additional factors that also play a role in failure of IVIG treatment²

- Young patient age, particularly less than one year
- Significantly elevated CRP
- Elevated liver enzymes
- Platelet count of less than 300,000/mm³
- Elevated band count
- Serum sodium less than 133 and a low serum albumin

The choice of treatment post IVIG failure is important. If the patient remains febrile it increases the risk of developing coronary artery aneurysm. Journals from American Heart Association (AHA) advice for a 2nd dose of IVIG 2g/kg.⁵ A study by Burns et al showed that patients receiving another dose of IVIG of 2g/kg as compared to 1g/kg showed a reduced incidence of development of coronary artery disease.¹

In our patient however we opted to start the patient on IV methylprednisolone 30mg/kg for three days.

The inflammatory marker i.e., ESR remained high along with size of the coronary arteries six weeks after the initial diagnosis. Kawasaki disease which is refractory to IVIG has been shown to have increased incidence of coronary artery dilatation.

There is no consensus for the mode of treatment of refractory KD. Usage of corticosteroid have been suggested in which they inhibit the phospholipase A2 which is needed for production of arachidonic acid and inflammatory markers, this remains controversial. A study done by Furukawa et al,⁵ a second dose of IVIG compared to IV methylprednisolone in 63 cases of refractory Kawasaki disease. Of the 63 patients, 44 were given IV methylprednisolone (30mg/kg/day) for three days and 19 of them were given a second dose of IVIG 1-2g/kg. The results showed that patients treated with IV methylprednisolone had a faster resolution of fever and all were afebrile within one day.

However, at such high doses the chances of side effects increase. A study by Zhu et al., noted that five patients developed hypertension, three developed hypothermia and three developed sinus bradycardias with one developing transient fibular nerve palsy.

Other modes of treatment of Refractory Kawasaki Disease includes cyclosporine A, tacrolimus and infliximab had also been found to be safe and effective.

CONCLUSION

The diagnosis of Kawasaki disease has always been a clinical based diagnosis. The investigation and radiological evidence act merely to aid the physician in the diagnosis. A case of Refractory Kawasaki disease carries with it the same challenges. In both form of the disease the main aim is to prevent the development of a coronary arterial lesion (CAL). The approach as well as management and treatment of Kawasaki disease has been well established and documented. We in Hospital Seri Manjung have been successful in tackling cases of Kawasaki disease thanks in large to these guidelines. However, in the case of Refractory Kawasaki disease a number of hurdles cropped up be it in the form of treatment as well as choice of medication and observation.

This was particularly challenging as Hospital Seri Manjung is a district hospital with general pediatrician.

The reason for publishing a report of a case of Refractory Kawasaki disease is mainly to highlight the challenges that share the experiences faced in managing a case of Refractory Kawasaki disease in a district setup. We also hope this will spur a discussion for a more comprehensive set of guidelines in the management of Refractory Kawasaki disease.

REFERENCES

1. Burn JC, Kushner HI, Bastian JF, Shike H, Shimuzu C, Masturbara T, et al. Kawasaki Disease: A Brief History. *Paediatrics* 2000; 106(2): E27.
2. Do YS, Kim KW, Chun JK, Cha BH, Namgoong MK, Lee HY . Predicting factors for refractory Kawasaki Disease. *Korean Circ J* 2010; 40(5): 239-42.
3. Saneeymehri S, Baker K, So TY. Overview of pharmacological treatment options for paediatric patients with refractory Kawasaki Disease. *J Pediatr Pharmacol Ther* 2015; 20(3): 163-77.
4. Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, et al. Diagnosis and Treatment of 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. *Circulation* 2004; 110(17): 2747-71.
5. Furukawa S, Matsubara I, Motohashi T, Tsuda M, Sugimoto H, Yabuta K. Immunological abnormalities in Kawasaki Disease with coronary artery lesions. *Acta Paediatr Jpn* 1991; 33(6): 745-51.