INTRODUCTION

Kawasaki disease is an autoimmune vasculitic (medium blood vessel) disease of unknown aetiology found predominantly in children under 5 years affecting the skin, eyes, mucous-membrane, lymphnode, and extremities. Intravenous immnoglobulin and aspirin are enough to cure most patients, however some cases, have been shown to be refractory to this treatment with striking predilection for coronary artery dilatation and will require further management with corticosteroid, immunomodulatory or cytotoxic agents.

Multiple uncertainties exist related to the management of refractory KD despite the wide spectrum of therapeutic options that have been proposed. The arrangement of medical board and parents counselling are very important issue also. Our case shows that in patients refractory to initial IVIG therapy, monoclonal antibody (injection infliximab) infusion can be a reliable choice.

ABSTRACT

Kawasaki disease is an autoimmune vasculitic (medium blood vessel) disease of unknown aetiology found predominantly in children under 5 years affecting the skin, eyes, mucous-membrane, lymphnode, and extremities. Intravenous immnoglobulin and aspirin are enough to cure most patients, however some cases, have been shown to be refractory to this treatment with striking predilection for coronary artery dilatation and will require further management with corticosteroid, immunomodulatory or cytotoxic agents. Multiple uncertainties exist related to the management of refractory KD despite the wide spectrum of therapeutic options that have been proposed. The arrangement of medical board and parents counselling are very important issue also. Our case shows that in patients refractory to initial IVIG therapy, monoclonal antibody (injection infliximab) infusion can be a reliable choice.

INTRODUCTION

In 1961, Dr. Tomisaku Kawasaki (Japanese Paediatrician) first recognized and described what is known as Kawasaki disease. In 1976 a case report was published in the Japanese Literature. In 1974 first case was reported in English Literature. In 1976 first case reported from outside Japan (Hawaii). This autoimmune disease is described as an acute inflammation of the vasculature bed characterized by symptoms such as persistent fever, distinct erythema of the lips and oral mucosa, rash involving the trunk and extremities, bilateral non-purulent conjunctivitis and unilateral lymphadenopathy. Most of the time the disease is found to be acute and self-limiting however upto one quarter may develop coronary artery aneurysm, myocardial infarction which can lead to death.\(^1\)\(^2\)

An infectious agent may trigger an immunologic response in individuals who are at high risk, but a single infectious agent has yet to be identified.\(^1\)\(^2\) A genetic predisposition may play a role in the pathogenesis of this disease due to its high incidence in a particular region of the world and trends in genetic polymorphisms. Children who are born from parents with Kawasaki disease have twice the risk of having this disease in their lifetime.\(^3\) Patients with a variant or polymorphism in the inositol-triphosphate 3-kinase C (ITPKC) gene or the Fc fragment of IgG low-affinity II-a receptor (FCGR2A) gene have increased susceptibility to KD.\(^6\) The ITPKC gene plays a role in inhibiting T-cell activation and the FCGR2A gene plays a role in the function of IgG.\(^6\) Reduction in ITPKC expression leads to enhanced T-cell activation and thus increase interleukin-2 (IL-2) which in turn plays a role in the development of KD.\(^7\) Patients with this genetic polymorphism are also found to be at higher risk of developing coronary artery lesion and unresponsiveness to IVIG therapy.\(^7\)

Treatment is directed toward the reduction of inflammation of the vasculature beds and includes high dose aspirin in combination with a single infusion of IVIG. This combination reduces the length of fever and the incidence of coronary artery aneurysms.\(^8\) If given within 10 days of disease onset, this therapy reduces the risk of developing cardiac sequeale at 1 to 2 months from 20% to 25% to an incidence of 2% to 4%.\(^9\) In a number of patients, disease may be refractory to initial therapy and require further management with Immunomodulatory (injection infliximab) and cytotoxic agents and as well as corticosteroid.\(^1\)\(^3\)

Informed Consent was obtained from the patient’s father prior to the publication of this case report.

CASE REPORT

A 10 months 26 days old Bangladeshi boy, 2nd issue of his non-consanguineous parents got admitted to central hospital on December 23, 2018 through OPD having the complaints of...
high grade continued type of fever for 3 days associated with anorexia, vomiting, loose stool and bad odor from mouth cavity. Vomiting which was mainly after feed, non-projectile, nonbilious and loose stool which was => 5-6 times/day, soft, greenish yellow not mixed with blood.

On Examination: Baby was irritable, toxic, not dehydrated, had erythema of the lips and oral mucosa, bilateral non-exudative conjunctival injection, also had right sided cervical lymphnode enlargement, others HEENT was NAD. His vitals were pulse 124/min regular, Resp. rate-58/min, temperature 103°F, O₂ saturation was 95% in room air.

Other systemic examination had nothing abnormality detected.

On 22 December, 2018 (Day before admission): CBC, Blood CIS, urine RE+C/S, Dengue NS1 Antigen were given for evaluation of the patient by OPD doctor which showed negative for dengue NS1 Antigen and had neutrophilic leukocytosis with pyuria.

On 23 December, 2018 (Day 1): After admission an IV channel was opened and injection ceftriaxone was started for suspected UTI with Bacteremia, other symptomatic drugs were started as well.

On 24 December, 2018 (day-2): Baby developed skin rash so injection ciprofloxacin was discontinued and injection ceftriaxone and injection amikacin were started.

On 25 December, 2018 (day-3): Investigations were reviewed again and co-relating with the clinical features, patient went in favour of Kawasaki Disease. Aspirin was added to the current treatment and advised for IVIG infusion.

On 26 December, 2018 (day-4): We started injection immunoglobulin (IVIG) 2gm/kg single dose over 12 hours along with aspirin and other symptomatic drugs.12

From 27 December, 2018 to 28 December, 2019 (day-5 to 6): About 24 hours after completion of IVIG there was no change of patient’s condition. Fever persisted and the patient became so restless that meningitis was suspected and antibiotics were changed to injection meropenem, vancomycin, acyclovir and injection oraladroxone was also added. Simultaneously ECHO color Doppler and lumen puncture was done. C.S.F report showed cell count 20 cells/cumm (all are lymphocytes), sugar 64.0 mg/dl, protein: 67.30 mg/dl and ECHO doppler study showed mildly dilated LCA origin. Size = 2.6 mm (z-score 2.29). Normal origin RCA. Size: 2.00 mm.

From 29 December, 2018 to 4 January, 2018 (day-7 to 13): patient remained afebrile for two days but developed fever again from 31 December, 2018. Since there was no improvement in the patient’s condition, all antibiotics were discontinued on 03, January, 2019 after 7 days completion of above mentioned antibiotics. All investigations were reviewed and co-relating with his clinical conditions refractory KD was diagnosed, then decision was taken to give injection infliximab (monoclonal antibody) in a medical board meeting held on 04 January, 2019.

On 05 January, 2019 (Day-14): Injection infliximab (remicarid) was given 5 mg/kg, and in few hours fever subsided without any complication. However, there was excessive sweating in the end of injection infliximab administration.

On 07 January, 2019 (Day-16): Baby was discharged with advice.

In table 1 & 2 The Serial laboratory report that guided us for the management of the patient.

Three weeks after the discharge (on 21 January, 2019) ECHO colour doppler showed normal coronary artery. The prognosis of the disease was monitored by serial/repeated CBC, CRP, ESR and platelet count.

Dose of aspirin was reduced to 5mg/kg/day (as antiplatelet dose).

He was also consulted by a paediatric cardiologist and paediatric Rheumatologist and referred to paediatric Rheumatology department, BSMMU for future follow up

Table 1 Date wise laboratory report

<table>
<thead>
<tr>
<th>Date</th>
<th>WBC</th>
<th>Hb%</th>
<th>Platelet</th>
<th>ESR 1st hr</th>
<th>CRP</th>
<th>S. Albumin</th>
<th>S. Ferritin</th>
<th>Blood CS</th>
<th>Urine CS</th>
</tr>
</thead>
<tbody>
<tr>
<td>22/12/18</td>
<td>11,800/cumm N=82, L=14, E=2, M=2</td>
<td>10.8 mg/dl</td>
<td>320 K/L</td>
<td>0.33 mm</td>
<td></td>
<td></td>
<td></td>
<td>48 mg/L</td>
<td>No Growth</td>
</tr>
<tr>
<td>23/12/18</td>
<td>S. Electrolytes: Na=143mm/L, K=4.0mm/L, Cl=105mm/L, CO₂=24</td>
<td></td>
<td></td>
<td></td>
<td>48 mg/L</td>
<td></td>
<td></td>
<td></td>
<td>E.coliX10⁴ sensitive to ceftriaxone and amikacin</td>
</tr>
<tr>
<td>25/12/18</td>
<td>18,300 N=80%, L=14, E=2, M=4</td>
<td>9.5 mg/dl</td>
<td>225 k/L</td>
<td>60mm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No Growth</td>
</tr>
<tr>
<td>27/12/18</td>
<td>17,300 N=68%, L=28, E=2, M=2</td>
<td>S.Omg/dl</td>
<td>325 k/L</td>
<td>48 mg/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C.S.F. Culture No growth Bacterial antigen negative</td>
</tr>
<tr>
<td>31/12/18</td>
<td>13,500 N=77%, L=18, E=2, M=3</td>
<td>8.5 mg/dl</td>
<td>710 k/L</td>
<td>108mm</td>
<td>48 mg/L</td>
<td>20.1 gm/L</td>
<td>403 ng/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>05/01/19</td>
<td>14,400 N=48%, L=42, E=1, M=4</td>
<td>8.1 mg/dl</td>
<td>946 k/L</td>
<td>95mm</td>
<td>48 mg/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2 Serial laboratory findings in recovery phase

<table>
<thead>
<tr>
<th>Date</th>
<th>WBC</th>
<th>Hb%</th>
<th>Platelet</th>
<th>ESR in 1st hr</th>
<th>CRP</th>
<th>S. Albumin</th>
<th>S. Ferritin</th>
</tr>
</thead>
<tbody>
<tr>
<td>21/01/19</td>
<td>12,000/cumm N=33, L=54, E=4, M=7</td>
<td>11mg/dl</td>
<td>390 K/L</td>
<td>35 mm</td>
<td>0.87 mg/L</td>
<td>36 gm/L</td>
<td>93.36ng/ml</td>
</tr>
<tr>
<td>25/02/19</td>
<td>14,000 N=35%, L=59, E=3, M=3</td>
<td>11.6mg/dl</td>
<td>530 k/L</td>
<td>36mm</td>
<td>0.98 mg/L</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
KD is really a challenging issue in paediatrics regarding both the diagnosis and management especially in case of refractory KD.

Recent study suggested that innate immune cells have the ability to develop a memory with significant implications in the host response to pathogens and auto immune disorder.

Refractory KD exist in 9.4% to 23% of patient treated with initial aspirin and IVIG therapy. Patients are considered to have refractory disease if they develop or continue to have fever within 36 hours of IVIG infusion. These patients are at increased risk of developing cardiac abnormalities and will need additional treatment.

Even though refractory KD is usually associated with CAA. There are no clear factors available to predict its development. However, different scoring system have been defined to predict non-responsiveness to initial IVIG therapy.

Several risk factor were identified which favour the development of CAL including Age, Sex, duration of fever, high ferritin level, delay in diagnosis and treatment etc.

Early diagnosis of KD is sometime difficult because of similarity between its clinical appearance and that of other infectious diseases. Therefore in these cases, ECHO color Doppler can be helpful.

A normal ECHO cardiography within the first 7 days of fever cannot rule out KD but positive findings can confirm the diagnosis. The management of refractory KD has not yet been clearly established. Multiple therapeutic options of refractory KD exist including a 2nd dose of IVIG or initiation of new therapy such as infliximab, corticosteroid, cyclosporin, cyclophosphamide or methotrexate.

In our case we preferred to administer injection infliximab. A study was done in 2018, published in int. j cardio regarding effective infliximab therapy for the early regression of coronary artery aneurysm in KD.

Infliximab is a monoclonal antibody that binds to and inhibits tumour necrosis factor-alpha (TNF-α ) which is responsible for inducing interleukins and proinflammatory cytokines, enhancing the migration of leukocytes and activating neutrophils and eosinophils. TNF-α inhibitors can reduce the inflamations associated with KD. TNF-α plasma concentration and soluble TNF receptor concentration are increased during the acute phase of Kawasaki disease and are associated with the development of coronary artery dilation/aneurysm.

Son et al (N=106): In a retrospective study of 106 patients who were resistant to initial IVIG therapy the use of infliximab was compared to the use of a 2nd dose of IVIG. 20 patients were treated with infliximab 5mg/kg and 86 patients were treated with 2nd dose of IVIG, 2g/KG. The patient treated with infliximab had a significant reduction in the days of continued fever (8 days vs 10 days respectively, p = 0.028) and a significantly shorter hospital stay. (5.5 days vs 6 days respectively p= 0.04). The majority of the patients responded to the study drug and did not require retreatment (85% infliximab vs 76% 2nd dose of IVIG. P=55).

Burns et al (N=24): Burns et al published a prospective randomized trial in 24 patients with disease refractory to initial IVIG treatment. The study compared the safety, tolerability and pharmacokinetics of infliximab with those of a 2nd dose of IVIG.

Mori et al: (N=20) In an open-label case series report, 20 patients resistant to large dose of IVIG therapy, upto 4gm/kg, were treated with 5mg/kg of injection infliximab. They were evaluated 48 hrs after the infusion for signs and symptoms of improvement and again at 30 days with an echocardiogram. All 20 patient showed mild dilation in their coronary arteries on the baseline echocardiogram. After the infusion 18 of 20 patients had a rapid decrease in their temperature within 24hr and a gradual decrease in other symptoms within 3 days.

It also provided anti-inflammatory effects over 3 days after the infusion. At the 30-days examination, 1 of the patients had a coronary artery lesion but had complete regression at one year. No adverse effects were reported in the patients treated with infliximab.

CONCLUSION

Kawasaki disease is purely clinical based diagnosis. The laboratory and ECHO doppler evidence can help to some extent. The aim of treatment of KD (both classical and refractory) is to prevent coronary artery dilatation. It is a great challenge for the clinician when it comes to counselling parents and providing appropriate management.

Early diagnosis and early start of treatment may decrease the morbidity and mortality. Current treatment options for refractory KD/incomplete KD are based mainly on observational study and case report.

The purpose of publishing this case report is to share the challenges associated with the management of refractory KD diagnosed in an infant at Central Hospital Ltd., Dhaka.

**Abbreviations:** KD= Kawasaki Disease, IVIG= Intravenous immunoglobulin, LCA= Left Coronary Artery, RCA= Right Coronary Artery, CRP= C-reactive protein, ESR= Erythrocyte Sedimentation Rate, BSMMU= Bangabandhu Sheikh Mujib Medical University. CAA= Coronary artery aneurysm, NAD= Nothing abnormality detected, CAL= Coronary Artery lession, HEENT = Head, Eye, Ear, Nose, Throat.

**References**


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**How to cite this article:**

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