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Case Report

Infliximab as a rescue therapy in the management of refractory typical infantile Kawasaki disease



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been described to have atypical, prolonged and severe manifestations of KD, which is commonly refractory to standard therapy. We herein describe KD in a 3-month-old infant patient who was diagnosed and treated early with infliximab as the alternative rescue therapy, which produced dramatic clinical response.

Case report

A 2.5-month-old female infant patient was brought to our hospital with complaints of high-grade fever of 2 days duration, macular rash most prominent over the upper part of body, extreme irritability and severe diarrhoea. There was no history of seizures, lethargy, increased chest activity, or abdominal distension. On examination, she was found to be irritable with high-grade continuous fever. Initially, she was managed as a case of sepsis, with broad-spectrum antibiotics, despite which she continued to be symptomatic. At admission, she had anaemia (haemoglobin 8.9 gm/dl), polymorphonuclear leucocytosis (total leucocyte count 17,600/mm³ with 85% neutrophils), normal platelet count and raised C-reactive protein (CRP; 24 mg/L) and erythrocyte sedimentation rate (ESR; 34 mm/h). Cerebrospinal fluid analysis was normal. Other workup including urine and blood cultures and abdominal ultrasonography was normal. She showed poor response to the therapy (including up to gradation of parenteral antibiotics), in view of which, an alternative diagnosis was sought. On the 4th day into illness, she was noticed to

Introduction

Kawasaki disease (KD) is an acute febrile illness of childhood characterised by vasculitis of medium-sized arteries, with special predilection to affect the coronary arteries. It was first described by Dr. Tomisaku Kawasaki in Japan in 1967.¹ The coronary artery involvement and cardiac morbidity were subsequently realised in the autopsies conducted on patients with KD. Since then, the world over, KD has been recognised as a leading cause of acquired heart disease especially in the developed countries, with higher incidence in Japanese children. KD is rare in infants aged <6 months. These infants have

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have right-sided non-tender cervical lymphadenopathy measuring 1.5 cm × 1.5 cm, bilateral non-purulent conjunctivitis and erythema over lips and tongue. A day later, the patient also developed extensive perineal desquamation (Fig. 1). At this stage, a possible clinical diagnosis of KD was entertained. The ESR and CRP showed rising titres (48 mm/h and 60 mg/L respectively, on the 5th day of illness), and thrombocytosis (platelet count 4.2 Lac/mm³) developed. A two-dimensional echocardiography at this stage was normal. Standard dose (2 gm/kg) of intravenous immunoglobulin was infused over 12 h to which she showed only partial response in terms of defervescence. In view of this, a second dose of Intravenous immunoglobulin (IVIG) (2 gm/Kg) was administered along with antiinflammatory dose of acetyl salicylic acid (100 mg/kg). However, she exhibited poor clinical response and continued to be febrile. At this stage (early 2nd week into illness), she developed desquamation of the skin of hands and feet. Repeat haematological parameters revealed worsening anaemia (Hb 7.9 gm%), polymorphonuclear leucocytosis (total leucocyte count 34,600/mm³), thrombocytosis (platelet count 5,71,000/mm³) and hypoalbuminemia (serum albumin 2.2 gm/dl). Peripheral blood smear showed a shift to the left and vacuolation in the leucocytes. A repeat echocardiography also revealed no abnormality. Thrombocytosis showed increasing trend in the ensuing 2 days. In view of no significant clinical improvement, she was administered Inj methylprednisolone 30 mg/kg for 3 days, following which, although she remained afebrile for 48 h, the fever recurred, later in the second week into illness. Inj infliximab (5 mg/kg) was then administered as a rescue measure, following which she became afebrile within 24 h, with no recurrence of fever thereafter. A repeat echocardiography at this juncture (at the end of the 2nd week) revealed large coronary aneurysms involving right coronary arteries (RCAs), left main coronary arteries (LMCAs), left anterior descending coronary arteries (LADCA) and left circumflex coronary arteries (LCxCA) (Fig. 2), normal biventricular systolic and diastolic function and mild pericardial effusion. The 12-lead electrocardiogram was normal. Oral steroid and injection of low-molecular-weight heparin were also added. After discharge, serial echocardiography studies on follow-up revealed gradual and significant reduction in the size of coronary artery aneurysms (CAAs) after 3 months and complete regression after 12 months (Table 1). She was continued on antiplatelet dose of acetyl salicylic acid throughout the follow-up.

Discussion

Kawasaki disease is an idiopathic multisystem disease involving acute vasculitis of mainly medium-sized vessels, characteristically the coronary arteries. It is the commonest cause of acquired heart disease in children in the USA and Japan. In majority of cases, it affects children aged between 1 and 4 years and is rare in young infants and children older than 10 years. Over the last 20 years, KD is being increasingly recognised in India, and it may soon replace acute rheumatic fever to become the commonest cause of acquired heart disease among children.³ There is paucity of Indian data on KD in young infants. Although clinical diagnostic criteria exist for diagnosing typical KD, atypical form of the disease may have incomplete clinical picture.

The aetiology of KD remains an enigma even though the disease has been known for more than 50 years. Various aetiological factors such as genetic, immunological and infectious agents (New Haven coronavirus, Epstein–Barr Virus, Bocavirus, adenovirus and *Yersinia pseudotuberculosis*) have been implicated. Probably, there is interplay of many factors, such as role of an infectious agent in a genetically susceptible host.⁴

The youngest patient reported is a 2-week-old neonate. With a reported incidence of KD in infants younger than 6 months being 7.7%–11.2%, the disease is extremely rare in infants younger than 3 months with incidence of 1.7%.⁵ Patients younger than 1 year have more frequent high white blood cell count and sterile pyuria but less neck lymphadenopathy.⁵ Because many infants present atypically, KD should be considered in all children aged 1 year or less with prolonged fever, extreme platelet count elevation and no compelling alternative diagnosis. Infants younger than 6 months with prolonged unexplained febrile illnesses should be suspected as having KD despite the incomplete clinical presentation. They may have rare clinical features including abdominal pain, diarrhoea, vomiting, upper respiratory tract infection, sterile pyuria⁶ and, very rarely, intussusception and hydrops of the gallbladder.^{5,7}

The atypical presentation in our patient included diarrhoea and features suggestive of sepsis. Our patient also had typical cervical lymphadenopathy, incidence of which is found to be low in other studies. In one of the studies, longer duration of fever and incomplete clinical manifestations in infants were

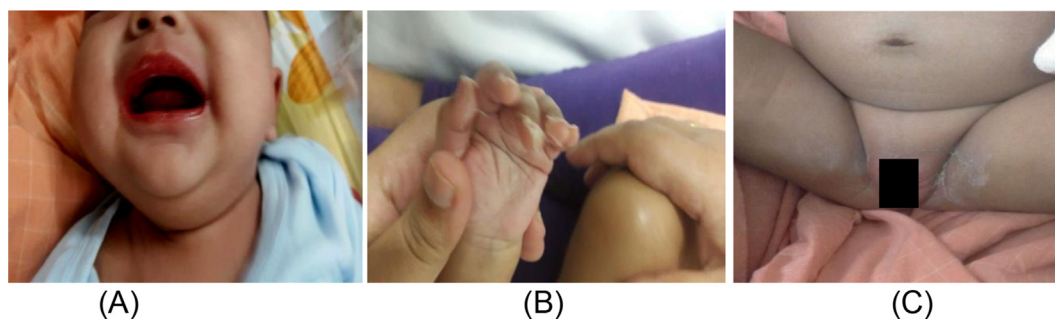


Fig. 1 – (A) Typical oral erythema, (B) changes (desquamation) involving the skin of extremities and (C) perigenital skin changes in our patient.

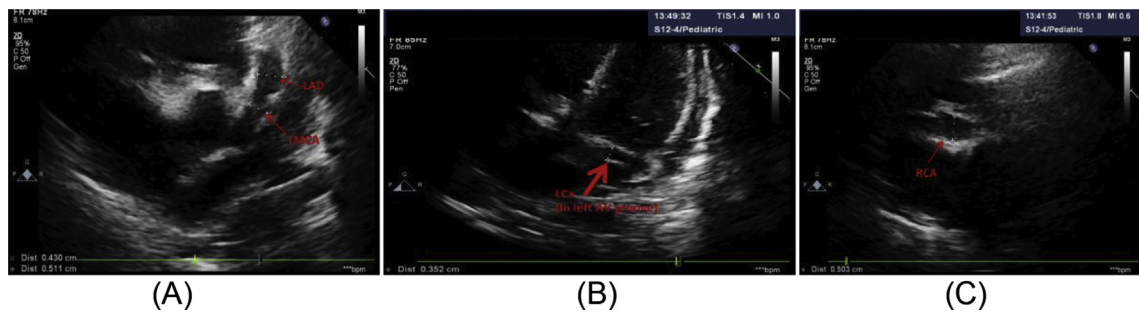


Fig. 2 – Dimensional transthoracic echocardiography images showing large aneurysms involving (A) Left main coronary artery (LMCA) and left anterior descending coronary artery (LADCA) (B) Left circumflex coronary artery (LCxCA) (C) Right coronary artery (RCA).

Table 1 – Baseline and follow-up trend of size and z-scores of coronary artery aneurysms.

| Site of coronary artery aneurysm | Dimension (mm) of aneurysm | | | | z-score* (Corrected for weight and length of patient) | | | |
|----------------------------------|----------------------------|------|------|------|---|-------|-------|-------|
| | At onset | 3 m | 6 m | 12 m | At onset | 3 m | 6 m | 12 m |
| Mid RCA | 5.03 | 3.20 | 2.60 | 2.0 | +12.78 | +6.43 | +4.11 | +1.81 |
| LMCA | 4.30 | 3.80 | 3.50 | 2.8 | +8.93 | +6.86 | +5.42 | +2.72 |
| LADCA (Largest aneurysm) | 5.11 | 2.70 | 2.40 | 2.0 | +13.43 | +4.95 | +3.56 | +1.78 |
| LCxCA | 3.52 | 2.14 | 2.01 | 1.9 | +8.19 | +3.26 | +2.44 | +1.58 |

*z-scores as per data by Dallaire et al., 2010 at Montreal, Quebec, Canada.²

LMCA, left main coronary artery; LADCA, left anterior descending coronary artery; LCxCA, left circumflex coronary artery; RCA, right coronary artery.

significantly associated with development of coronary artery abnormalities.⁸

The hallmark of KD is involvement of coronary arteries. Although all the clinical features of KD resolve after acute illness, the risk of developing CAAs is approximately four times higher in children who do not receive the standard IVIG treatment (20–25% vs 4–6%).⁹

Therefore, the primary aim of all the treating physicians should be early recognition of KD and administration of IVIG and consideration of alternative therapy if there is poor response to standard treatment. Different scoring systems are described to identify the patients at high risk of unresponsiveness to IVIG therapy.

Despite early treatment with IVIG, 10–20% of patients with KD do not show any response after the first dose of IVIG. These patients are offered repeat doses of IVIG. Of these, 3–4% patients would still be refractory to treatment. Guidelines from the American Heart Association recommend a second dose of IVIG, methylprednisolone, a longer tapering course of prednisolone or prednisone plus IVIG, infliximab, cyclosporine, immunomodulatory monoclonal antibody therapy, cytotoxic agents or plasma exchange for patients resistant to IVIG.¹⁰

Patients treated with infliximab have demonstrated fall in the inflammatory markers [interleukin (IL)-6, TNF α], with corresponding reduction of fever, without adverse effects. Infliximab is a chimeric mouse-human monoclonal antibody directed against soluble and membrane-bound tumour necrosis factor- α .

However, in their randomised control trial, Adriana et al. demonstrated that addition of infliximab to standard therapy in patients with typical KD (4 weeks–17 years) did not reduce the treatment resistance, but it did reduce the fever duration,

inflammatory markers and more importantly the risk of developing LAD CAAs.¹¹

Case reports have demonstrated its superiority over IVIG in terms of reduction of fever duration, although a similar role in prevention of CAAs has been questioned. The recommended dose of infliximab is a dose of 5 mg/kg infusion i.v. once a day over 2 h, for 1–3 days.¹²

In our case, infliximab was administered after failure of response to two doses of IVIG and to methylprednisolone.

Conclusion

Infliximab is emerging as an alternative therapy with good clinical response in patients who are refractory to standard therapy. However, larger adequately powered trials are required to recommend infliximab therapy as an early alternative to second dose of IVIG in resistant infantile cases of KD and to prevent CAAs.

Conflicts of interest

The authors have none to declare.

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