

Double Coronary Aneurysms in Kawasaki Disease Successfully Treated with Anakinra: A Case Report

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Abstract

Background: Kawasaki disease is an acute inflammatory vasculitis of the medium and small-caliber arteries, usually occurring in children under 5 years of age. It is known to cause coronary aneurysms, which are more frequent in refractory forms. While the treatment of classical Kawasaki disease is well codified, the treatment of refractory forms remains non-standardized. Anakinra, an interleukin-1 receptor antagonist, appears to be a promising therapeutic alternative.

Case Presentation: We report a case of 9 months old girl, diagnosed with Kawasaki disease, non-responsive to two doses of intravenous immunoglobulins and acetyl salicylic acid, who developed aneurysms, successfully treated with Anakinra 3 months with 5 years of follow-up.

Conclusions: Our experience highlights Interleukin-1 blockade effectiveness in reducing Kawasaki disease systemic inflammation. We believe that our case adds more evidences to the potential role of interleukin-1 receptor antagonist as second or third-line therapy in some cases of refractory Kawasaki disease, particularly with severe involvement of coronary arteries.

Keywords: Anakinra; Coronary Arteries; Kawasaki Disease

Abbreviations: CAA- Coronary Artery Aneurysms; IL- Interleukin; IVIG- Intravenous Immunoglobulin; KD- Kawasaki Disease; LCA- Left Coronary Artery; LDCA- Left Anterior Descending Coronary Artery

Introduction

Kawasaki disease (KD) is an acute inflammatory vasculitis of the medium and small-caliber arteries, typically involving coronary arteries, usually occurring in children under 5 years, and represents the leading cause of acquired heart disease in developed countries and the second cause after rheumatic fever in some developing countries. The diagnosis of KD is based on the presence of high fever lasting at least 5 days associated with at least four of the five main features: peripheral extremity involvement, cervical adenopathy, bilateral non-exsudative conjunctivitis, cheilitis, and polymorphic skin rash [1]. The first-line treatment, a single infusion of 2 g/kg intravenous immunoglobulin (IVIG) along with aspirin, reduces coronary artery aneurysms (CAA) frequency from 25–30% to about 3-5% [1,2]. However, 10-20% of patients with KD are resistant to conventional therapy, putting them at significant risk for cardiac complications [3]. The role of interleukin (IL)-1 in the pathophysiology of KD and in the development of CAA is recognized although not well understood. This leads to the potential use of IL-1 blockade as an alternative therapy for refractory KD [4,5]. In this article, we report the

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case of a 9-month-old girl diagnosed with KD, refractory to two doses of IVIG, who developed aneurysms, successfully treated with Anakinra.

Case Report

We report the case of a previously healthy 9-month-old girl admitted for 8 days persistent fever at 39.7° on admission. She had asthenia, bilateral non-purulent conjunctivitis, cheilitis, right cervical lymphadenopathy measuring 2 cm and erythematous scaling perineal rash (Photo 1). The blood count cells showed normochromic microcytic anaemia (Hb:9.9 g/dL, MCV: 69 fl, MCHC: 34 g/dL), hyperleukocytosis at 17.3 G/L, hyperneutrophilia at 11.64 G/L, normal platelets at 289 G/L, elevated ESR at 122 mm/1st hour, increased C-reactive protein at 260 mg/L and subnormal transaminases (AST at 69 U/L, ALT at 33 U/L). The patient fulfilled the criteria of Kawasaki disease. She was treated with intra-venous polyvalent immunoglobulin "IVIG" at a dose of 2 g/kg/perfusion combined with aspirin at 50 mg/kg/d on the 9th day of fever. An echocardiogram performed on the 11th day of fever was normal. The persistence of fever led to a second echocardiogram on day 16 which revealed double aneurysmal dilatation of the left coronary artery (LCA) to 4.1 mm (Figure 1) and the left anterior descending coronary artery (LDCA) to 3.4 mm justifying a second IVIG infusion on the same day allowing apyrexia. A follow-up echocardiogram was performed on day 24 and showed a worsening of the aneurysm in the LCA to 6 mm and in the LDCA to 4 mm. The inflammatory screening showed a significant increase in platelets to 758 G/L, a persistent inflammatory syndrome with ESR of 40 mm/1st hour and a CRP of 74 g/dL. Due to this extensive coronary lesions and the persistent inflammatory syndrome, third-line treatment with Anakinra 5 mg/kg/day was started for a period of 3 months, combined with aspirin at 5 mg/kg/day leading to regression of the inflammatory syndrome. Subsequent echocardiograms at months 2 and 3 showed decreasing dilatation

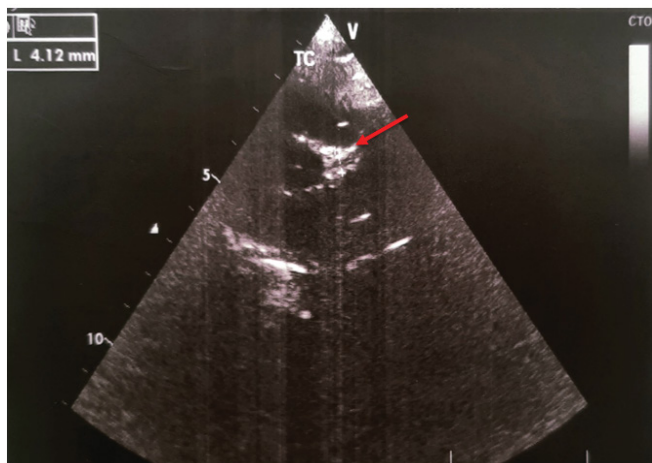


Figure 1: Transthoracic echocardiography revealed aneurysmal dilatation of the left coronary artery (4,1 mm with Z-score +5,8).



Figure 2: Last transthoracic echocardiography at year 4 revealed persistence of total resolution of aneurysm.



Photo 1: Erythematous scaling perineal rash.

of the aneurysms with complete normalization of cardio-vascular findings at month 8 allowing discontinuation of aspirin. No changes on coronary arteries size have been recorded over time with a current follow-up of 5 years (Figure 2).

Discussion

KD is a systemic vasculitis characterized by increased inflammatory cytokines, such as tumor necrosis factor α , Interleukin (IL) IL-6, and IL-1 [1]. IVIG represents the gold standard treatment and have significantly decreased the incidence of coronary involvement. In contrast, children that do not respond to initial IVIG have a higher risk of developing CAAs [6]. The pathogenesis of IVIG resistance is not well

Table 1: Case reports of Anakinra use in resistant Kawasaki disease.

Reference	Number of patients	Previous treatment	Reason for using Anakinra	Doses and duration of Anakinra	Outcome
[12]	1	1 IVIG 1 Steroid bolus	Macrophage activation syndrome	3 mg/kg/day 3 days then 8 mg/kg/day 5 months	Normalization of previous abnormalities
[13]	1	1 IVIG	Coronary aneurysms	4 mg/kg/day 2 months	Normalization of the Z score
[14]	1	2 IVIG, 3 Steroid boluses 1 Infliximab	Giant aneurysms	6 mg/kg/day 9 weeks	Progressive clinical improvement, Normalization of inflammatory markers, Resolution of aneurysms
[15]	11	At least 2 IVIG	Persistent fever, dilatation of coronary arteries, laboratory abnormalities myocarditis with KD shock syndrome	Range 2–8 mg/kg/day & 6-81 days	Resolution of fever, Reduction of inflammation indexes, and of the Z score
[16]	1	2 IVIG 4 Steroid boluses	Persistent fever and biological abnormalities	2 mg/kg/day 2 weeks	Normalization of clinical, biological and echography abnormalities
[17]	1	2 IVIG 1 Infliximab 3 Steroid boluses	Macrophage activation syndrome	5 mg/kg/day 1 day then 10 mg/kg/day tapering in 6 months	Gradual resolution of clinical symptoms, Normalization of laboratory tests
[18]	1	2 IVIG 3 Steroid boluses	Worsening of coronary aneurysms	6 mg/kg/day 10 weeks, Tapered to 6 mg/kg/every 2 days 4 weeks, tapered to 6 mg/kg/every 3 days 4 weeks	Apyrexia, Normalization of biological abnormalities, Reduction of aneurysms
[19]	1	1 IVIG	Coronary aneurysms and increased proBNP levels	100 mg/day 4 weeks	Resolution of clinical and biological abnormalities, Disappearance of the stenosis and persistence of slight dilatation only in the proximal portion of the main vessels
[20]	16	1 or more IVIG	Persistent fever, clinical and biological abnormalities	2mg/kg/day 4mg/kg in patients ≤ 8 months and ≥ 5 kg, increased up to 6mg/kg/d if temperature remained >38°C 14 days	Apyrexia, Reduction of disease activity, Normalization of CRP, Improvement of Z score

elucidated as the mechanism of action of IVIG is unclear. It appears that host genetic factors, such as polymorphisms in IG-binding gamma Fc receptors or copy number variation of FCGR2C, FCGR3A, and FCGR3B, may be involved in the response and resistance to IVIG [7,8]. Furthermore, an abundance of IL-1 α and β -related transcripts has been described in KD blood samples compared to pediatric subjects with different acute infectious diseases or healthy controls [9]. In addition, decreased IL-1 receptor antagonist expression has been reported in IVIG-resistant KD patients [10]. All this suggests that IL-1 excess seems to play a role in the occurrence of KD and in IVIG resistance. Thus, IL-1 blockade represents an attractive target because of its strong role in the pathogenesis of KD and CAAS [5]. Few previous studies reported the use of Anakinra in refractory KD cases; in most patients, it has been used as rescue therapy subsequently to the failure of multiple therapeutic strategies [11]. Anakinra administration was preceded or associated to further IVIG doses [12], Methylprednisolone pulses [11-13] Infliximab

[12,14] and Cyclophosphamide [13]. Anakinra appeared to be effective in achieving prompt defervescence and significant reduction of inflammatory markers [11,15,16]. Anakinra treatment showed a complete or partial improvement in most patients with KD who developed coronary complications [12-17]. The first report of anti-IL-1 use in KD dates back to 2012 and described a 2-year-old boy with classic KD who developed myocarditis, coronary artery inflammation and dilatation of the left descending coronary and right coronary arteries, despite 2 doses of IVIG and three boluses of methylprednisolone, who dramatically improved with Anakinra and normalized his cardiac ultrasonography after 6 months [11]. Several other cases have been published reporting the efficacy of Anakinra in refractory KD complicated by severe coronary aneurysms as shown in Table 1 [12-20].

Conclusion

Our experience provides an additional argument for prescribing Anakinra as a second or third-line treatment in some cases

of refractory Kawasaki disease, especially in cases of severe coronary artery involvement.

Authors' Contribution

KB conceptualized, and critically reviewed the manuscript for important intellectual content. SL is the resident who drafted the manuscript. AS is a permanent pediatric rheumatologist in the unit. AD did the echocardiographic follow up. All authors read and approved the final manuscript.

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Competing Interest

The authors declare that they have no conflict of interest.

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