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Successful Coronary Artery Aneurysm Reduction with Infliximab in a High-Risk Infant with IVIG-Resistant Kawasaki Disease

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Abstract

This case report describes the clinical course of a 3-month-old female with Kawasaki Disease (KD) who presented with intravenous immunoglobulin (IVIG) resistance and coronary artery aneurysm (CAA) complications. Following initial IVIG treatment at an outside hospital, the patient exhibited persistent inflammation and rapid progression of CAA, prompting referral to our institution. Infliximab, an anti-tumor necrosis factor (TNF)-α inhibitor, was administered, resulting in rapid improvement of inflammatory markers and CAA dimensions within five days. While there is currently no clear guidance on second-line treatment in refractory KD cases, a second dose of IVIG has generally been used. However, this case exemplifies the efficacy of infliximab in rapidly reducing inflammation and CAA risk, aligning with emerging evidence supporting the use of infliximab in cases resistant to initial IVIG treatment. This is notable, given the scarcity of clear guidelines for second-line treatment in refractory cases, particularly in infants. Early intervention plays a critical role in altering the disease course, underscoring the need for timely and appropriate treatment in high-risk KD patients.

Keywords: Infliximab; Kawasaki disease; IVIG resistance; Refractory Kawasaki disease; Coronary artery aneurysm

Introduction

Kawasaki Disease (KD) is an acute medium vessel vasculitis, often afflicting the coronary arteries, pre-dominantly affecting children younger than 5 years old [1]. The primary concern with refractory KD is the development of coronary artery aneurysms (CAA), which can lead to long-term cardiovascular complications, including myocardial infarction or sudden death. Initial treatment typically involves intravenous immunoglobulin (IVIG) to reduce inflammation and prevent coronary involvement [2]. However, approximately 10-20% of patients exhibit IVIG resistance, leading to persistent inflammation and an increased risk of CAA [2]. Management of IVIG-refractory KD remains challenging, with no clear robust data from clinical trials to guide second-line treatment [2].

Currently, the American Heart Association guidelines recommend a second dose of IVIG at least 36 hours after the end of the first IVIG infusion, of class IIa recommendation status with Level of Evidence B [2]. The American College of Rheumatology conditionally recommends a course of glucocorticoids as an alternative to second dose of IVIG [3]. Another option includes biologics like infliximab, a tumor necrosis factor (TNF)-α inhibitor. Infliximab, however, is currently written as a class IIb recommendation, with Level of Evidence C [2]. This case report describes the clinical course of a 3-month-old female with IVIG-resistant KD complicated by rapidly progressive coronary artery aneurysms and highlights the efficacy of early infliximab administration in controlling inflammation and reversing CAA progression.

Case Presentation

A 3-month-old female presented to our hospital following a recent diagnosis of Kawasaki disease and treatment with intravenous immunoglobulin at an outside hospital (OSH). 20 days prior to her presentation at our hospital, the patient experienced four days of fever up to 103°F. Subsequently, she developed an erythematous rash originating on the trunk, conjunctivitis, cracked lips, and redness on both hands and feet over four days.

Laboratory results on admission at OSH indicated findings consistent with KD: pyuria with a urine white blood cell count of 13 x 10^3 cells/µL, hemoglobin level of 11.2 g/dL (ref:10.4 -14.5) and hematocrit of 32.4% (ref:30.0-44.0), with leukocytosis of 17.2k WBC/high power field (hpf) (ref: 5.0k – 20.0k) and a platelet count of 466,000/µL (ref: 130k - 450k). Inflammatory markers were elevated, with a C-reactive protein (CRP) level of 97.1 mg/L (ref: < 5.0) and erythrocyte-sedimentation rate (ESR) at 49 mm/hr (ref: 0-14). A 2D echocardiogram performed 20 days prior to admission demonstrated normal findings, specifically a left main coronary artery (LMCA) of 1.9mm or Z-Score: +0.47, classified as no dilatation based on the American Heart Association guidelines [4].

The patient received intravenous immunoglobulin (IVIG) and was diagnosed with KD. The patient was discharged the following day as there was no recurrent fevers or symptoms and was given a daily regimen of 81mg aspirin. Three days after discharge from OSH and four days following the IVIG infusion, the patient continued to exhibit bilateral swelling around the eyelids and photosensitivity. She was evaluated by ophthalmology and prescribed a steroid eye ointment for inflammation. The patient was reported to experience an erythematous rash on her body for a week. She also maintained a lower temperature from 99°F to 100°F with reported fussiness. The patient returned two weeks later for a scheduled appointment at the OSH, where an echocardiogram demonstrated dilatation of the LMCA to 3.2mm and a Z-score of 4, classified as a small aneurysm. Plans were made for a repeat echocardiogram in one week at the same institution. Laboratory studies conducted on the same day demonstrated a decreasing trend in CRP levels to 7.3 mg/L (ref: <5.0) and ESR at 33 mm/hr (ref: 0-14). The patient had a hemoglobin of 10 g/dL (ref: 10.4-14.5), hematocrit of 29.7 (ref: 30.0 – 44.4), leukocyte count of 15 x 10^3/µL (ref: 5.0k – 20.0k) and platelet count of 635,000/µL (ref: 130k - 450k).

The family then contacted a KD support group, leading to a referral to our institution two days later. Upon arrival, vital signs showed low fever of 37.7°C, heart rate of 136 bpm, blood pressure at 88/66 mmHg, and a respiratory rate of 44 breaths per minute. Laboratory results indicated systemic inflammation, with a leukocyte count of 17.8 x10^3/µL (ref: 5.0k – 20.0k) and platelet count of 660,000/µL (ref: 130k - 450k). CRP and ESR were elevated at 9.2 mg/L (ref: <5.0) and 64 mm/hr (ref: 0-14) respectively, suggesting an active inflammatory response. The patient was admitted for management of IVIG-resistant Kawasaki disease.

An echocardiogram was ordered and revealed progression of dilatation of the LMCA, now a moderate aneurysm measuring 4.6mm and a Z-score of 6 from the previous small aneurysm (Z-score 4). Given the urgency to address the continued inflammatory process in this high-risk infant and evidence of persisting inflammation with residual coronary artery complication, a dose of 10 mg/kg infliximab was administered which was well tolerated with no adverse effects. Due to the progressive dilatation of the LMCA, dual antiplatelet treatment with clopidogrel and aspirin was initiated to decrease risk of thrombosis, which she remained on throughout the hospital stay. The patient's condition improved two days after the infliximab infusion, and she was afebrile and less fussy. A repeat echo showed improvement in LMCA with decreased dilatation (4.5 mm, Z-score 5.9).

The patient was monitored over 5 days and discharged once inflammation was under control. Repeat echo performed on day of discharge demonstrated improvement in LMCA, now measuring 4.2 mm, Z-score 5.4. Additionally, there was a significant improvement in the marker of inflammation, with the ESR dropping from 64 mm/hr to 26 mm/hr. Due to the patient’s dual antiplatelet therapy, hematology recommended a platelet function assay, demonstrating a 195 platelet function screening epinephrine and 124 platelet function screening ADP, consistent with appropriate antiplatelet therapy. Repeat lab work on the day of discharge showed decreasing CRP, decreasing ESR, and improving thrombocytosis. There was a slight increase in leukocyte count, likely attributed to the two-week use of topical steroid ointment on the eyelids. The patient was discharged on oral aspirin (3.75 mg/kg/day) and oral Plavix (0.4 mg/kg/day) once daily.

The patient returned for a follow-up visit 23 days after initial visit. At this time, echocardiogram demonstrated continued LMCA improvement to a measurement of 3.1mm, consistent with a Z-score of +3.4 and categorizing as a small aneurysm. 86 days after the initial visit, the coronary arteries regressed to a measurement of 2.5mm, Z-score of +2.0 and no longer reaching criteria for small aneurysm. She is continued on oral aspirin (3.75 mg/kg/day) daily with plan to discontinue aspirin in the future if the aneurysm continues to resolve.

Table 1: Timeline of Patient Inflammation and LMCA Dilatation Progression.

	Admitted to OSH - 20 days PTA	OSH Day 1 – 19 days PTA	2 days PTA	Admitted to Our Hospital	Hospital Day 1	Hospital Day 2	Hospital Day 5	23 Days after Admission	86 Days after admission
ESR (Ref: 3-13 mm/hr)	49 mm/hr	IVIG infusion 10g (2g/kg * 4.93 Dosing weight)	33 mm/hr	64 mm/hr	– Infliximab administered 10mg/kg/dose IV infusion on 9/14 at 3 am over 2 hours	N/A	26	8	-
CRP (Ref: <5)	84.2 mg/L		7.3 mg/L	9.2 mg/L		N/A	6.1	12.3 mg/L	-
WBC (Ref: 5.0k – 20.0k)	16.0k		15.0k	17.8k		N/A	20.6k	19.5k	-
Platelets (Ref: 140k-450k)	426k		635k	600k		N/A	586k	380k	-
2D Echocardiogram	LMCA Z-Score: +0.47, 1.9mm : no involvement		LMCA Z Score: +4.0, 3.2mm : small aneurysm	LMCA Z-Score: +6.0, 4.6mm : medium aneurysm		LMCA Z-Score: +5.9, 4.5mm : medium aneurysm	LMCA Z-Score: +5.4, 4.2mm : medium aneurysm	LMCA Z-Score: +3.4, 3.1mm; small aneurysm	LMCA Z-Score: +2.0, 2.5mm; normal;

Discussion

This case of a 3-month-old infant with IVIG-resistant Kawasaki Disease and rapidly progressing coronary artery aneurysm presents several critical elements that contribute to the ongoing understanding and management of high-risk KD patients. Not only does it demonstrate the efficacy of infliximab in a very young patient, but it also highlights the importance of early intervention and combination therapy in controlling the progression of CAAs in IVIG-resistant cases.

First, this case underscores the importance of stratifying risk in KD patients and identifying high-risk patients for IVIG-resistance and development of coronary artery aneurysms. The rapid progression of LMCA dilatation from a Z-score of 4 (small aneurysm) to a Z-score of 6 (moderate aneurysm) within a 2-day span underscores the severity of this patient's inflammation and risk of further complication. Such rapid progression highlights need for vigilant monitoring and intervention in high-risk cases. Age may serve as a significant indicator for identifying patients prone to cardiac symptoms, as demonstrated by this 3-month-old patient. This aligns with a study which revealed a higher incidence of infants under 6 months displaying dilated or aneurysmal coronary arteries on their initial echocardiogram compared to those older than 6 months (43.4% vs 19.5%) for patients treated within the first 10 days after the onset of fever [5].

Furthermore, the same study found that 18.6% of infants under 6 months, who presented with a normal echocardiogram at diagnosis, subsequently developed an aneurysmal coronary artery within 8 weeks of diagnosis [5] —similar to our case, wherein a patient exhibited a normal Z-Score of +0.49 to +4.0 within a span of 2.5 weeks. Age may be of consideration in predicting IVIG-resistance as well, with 3 countries (Italy, Spain, and Sweden) specifying <12 months as a risk factor associated with higher risk of being IVIG-resistant and/or risk of CAA and/or considered for intensified treatment [6]. The Kobayashi score used in Japan and adopted for Japanese patients in the U.S. additionally uses age <12 months as 1 point in prediction of IVIG-resistance [7]. Further studies are needed in the United States to identify high risk patients including young infants and determine if intensified treatment is associated with better outcomes.

In this case of high-risk patients, this case thus emphasizes the possibility of infliximab as improving coronary artery aneurysm outcomes in comparison to second dose IVIG. At this time, some experts generally recommend a second dose of IVIG to refractory KD patients [6], however, there is no clear guidance on second-line treatment, which may include second dose of IVIG, IV methylprednisone, or infliximab, an anti-tumor necrosis factor (TNF)-α inhibitor [8]. Etanercept (blocking TNF alpha) and anakinra, an interleukin 1 receptor antagonist, are also considered for third line treatment [6]. In this case, infliximab was effective in controlling the inflammatory process and mitigating the risk of further dilation of coronary arteries. This intervention is consistent with emerging evidence supporting its efficacy in IVIG-refractory cases in comparison to second dose of IVIG, where use of infliximab resulted in shorter duration of fever, reduced need for additional therapy, less severe anemia, and shorter hospitalization [9]. In a study of 43 IVIG-resistant children receiving second-line treatment, it was observed that 65.6% responded positively to IVIG retreatment, while 90.9% responded to infliximab, with the latter group experiencing shorter fever durations and fewer hospitalization days, however, no significant differences in coronary artery outcomes were noted [10].

A recent retrospective multicenter study conducted in Korea provided evidence supporting infliximab's positive impact on coronary artery outcomes, showing it to be generally well-tolerated and effective in reducing fever duration for patients, particularly when administered early after IVIG treatment, leading to fewer coronary artery complications in those with IVIG-resistant KD potentially due to decreased fever duration [8]. An indirect comparison meta-analysis by Chan et al. found no significant differences in the cardioprotective effect between infliximab, IVMP, and second IVIG infusion in refractory KD [11]. Further research is needed to identify the most effective second-line treatment for improving coronary artery outcomes, particularly with regard to whether treatment approaches should vary based on age. Our experience in this case supports these assertions that infliximab is a well-tolerated and effective therapeutic option in IVIG-refractory KD patients and was associated with decreased LMCA dilatation and inflammatory markers in our patient after her initial IVIG-resistant inflammation persisted.

Conclusion

In conclusion, a single dose of infliximab for the management of IVIG-resistant KD is effective and well tolerated in our young infant of 3 months. This case underscores the importance of recognizing and promptly addressing high-risk presentations of KD, particularly in cases demonstrating persistent inflammation and rapid progression of dilatation of coronary artery. Early intervention with infliximab has demonstrated its safety and efficacy, potentially averting severe cardiac complications. Although current guidelines often favor a second dose of IVIG as the standard second-line treatment, the evidence supporting infliximab in IVIG-refractory cases is growing, particularly in high-risk patients like this infant. The lack of clear guidance for second-line treatment underscores the significance of this case in demonstrating the potential of infliximab to manage refractory KD. This case adds to the growing body of evidence supporting infliximab as a valuable option for IVIG-refractory Kawasaki Disease, particularly in high-risk and young patients where early intervention is critical.

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