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CLINICAL CASE

Immunoglobulin-resistant Kawasaki disease

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Abstract

Background: *Kawasaki disease is a systemic vasculitis that affects small and medium-sized vessels, primarily the coronary arteries. First-line treatment includes intravenous immunoglobulin (IVIG) and acetylsalicylic acid; however, 20% do not respond adequately despite treatment. We describe a case treated with etanercept after initial IVIG failure, showing a good response.* **Case report:** *A 5-year-old female was diagnosed with classic Kawasaki disease. Echocardiography and angiotomography revealed giant and fusiform aneurysms in the coronary arteries. A first dose of IVIG therapy was administered without improvement; after the second dose, the fever persisted, so etanercept was administered, and the fever subsided. There were no new lesions in medium-caliber vessels and the previously identified coronary lesions did not progress.* **Conclusions:** *The use of etanercept in Kawasaki disease has demonstrated a clinically favorable response. Controlled clinical trials of this drug are needed to establish it as a formal therapy in cases of initial IVIG failure.*

Keywords: *Kawasaki disease. Therapeutic failure. TNFα. Etanercept. Case report.*

Enfermedad de Kawasaki refractaria a tratamiento con inmunoglobulina

Resumen

Introducción: *La enfermedad de Kawasaki es una vasculitis sistémica que afecta los vasos de pequeño y mediano calibre con predominio de las arterias coronarias. El tratamiento de primera línea incluye inmunoglobulina intravenosa (IGIV) y ácido acetilsalicílico; a pesar del tratamiento, el 20% de los pacientes no responden adecuadamente. Se presenta un caso tratado con etanercept debido a la falla inicial a IGIV, con buena respuesta.* **Caso clínico:** *Se trata de una paciente de 5 años de edad, a quien se diagnosticó con enfermedad de Kawasaki clásica. En ecocardiografía y angiotomografía se evidenciaron aneurismas gigantes y fusiformes en las coronarias. Se administró una primera dosis con IGIV, sin mejoría; después de la segunda dosis, la paciente persistió con fiebre, por lo que se administró etanercept, tras lo cual esta cesó. No aparecieron nuevas lesiones en vasos de mediano calibre y las lesiones coronarias previas no progresaron.* **Conclusiones:** *Con el uso*

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de etanercept se presentó una respuesta favorable clínicamente en la enfermedad de Kawasaki. Se requieren ensayos clínicos controlados con este fármaco para establecerlo como terapia formal en los casos de falla inicial a IGIV.

Palabras clave: *Enfermedad de Kawasaki. Falla terapéutica. TNFα. Etanercept. Reporte de caso.*

Introduction

Kawasaki disease, a vasculitic syndrome that occurs mainly in children under 5 years of age, is characterized by the involvement of small and medium-sized arteries, particularly the coronary arteries[1]. The clinical diagnosis is based on four of the following five criteria: persistent fever of 5 days or more, non-exudative bulbar conjunctivitis, polymorphous generalized erythematous exanthema, oropharyngeal mucosal changes (raspberry tongue), unilateral cervical lymphadenopathy, and edema of the extremities followed by desquamation[2]. If left untreated, 25% of affected children develop serious complications such as coronary artery aneurysms. For this reason, pharmacologic treatment should be initiated as soon as the clinical diagnosis is made, preferably within the first 10 days after the onset of signs and symptoms, as the risk of complications is higher after this period.

First-line treatment is intravenous immunoglobulin (IVIG) and acetylsalicylic acid to reduce vasculitis and fever rapidly; however, up to 20% of patients are refractory to this treatment[3]. Patients are considered refractory or resistant to IVIG if fever persists or worsens 36 h after completion of the first dose of IVIG[4].

This refractoriness has prompted the search of new therapeutic options and adjuvants to reduce the rate of side effects. One option to consider is tumor necrosis factor alpha (TNF-α) blockers, which have been shown to reduce first-line resistance by up to 14-62% and infusion reactions by 55-99%[5]. Etanercept has been studied as an adjuvant and has shown to reduce the rate of resistance to IVIG and the progression of coronary artery lesions and dilations[6]. There is limited worldwide experience with etanercept in children, with results that appear to benefit specific age and race subgroups, particularly African-American children and those older than 1 year[7]. Given the frequency of first-line treatment failure, it is necessary to accumulate information regarding the usefulness of TNF-α blockers. We present the case of a patient who did not respond to initial treatment with intravenous gamma globulin and responded to etanercept therapy.

Clinical case

We describe the case of a female patient aged 5 years and 9 months, with no family health history relevant to the present condition. She was admitted to the hospital with an illness of 8 days, beginning with a fever between 39 and 40° C, irritability, pharyngodynia, and cervical pain secondary to visible bilateral lymphadenopathy. Three days before admission, she showed a non-exudative conjunctival injection, genital erythema, generalized myalgias, and desquamation of hands and feet. Before admission, she visited a physician who prescribed antibiotic therapy and anti-inflammatory drugs. It was decided to admit her to the hospital for evaluation and diagnostic protocol. Admission laboratory studies revealed thrombocytosis (total platelets 728,000/mL), in addition to elevated acute phase reactants (erythrocyte sedimentation rate [ESR] 95 mm/h and C-reactive protein [CRP] 12.79 mg/dL) (Table 1).

After admission, treatment initiated with 200 mL of Rubin Calcagno solution for 24 h, human immunoglobulin (Octagam®) infusion 2 g/kg/day for 12 h, acetylsalicylic acid 50 mg/kg/day fractionated in three doses, clopidogrel 4 mg every 24 h, omeprazole 20 mg every 12 h, and paracetamol (acetaminophen) 240 mg (if necessary). Because of the suspected diagnosis of Kawasaki disease, angiotomography of the coronary arteries was performed (Figure 1).

The study was performed on a 128-channel dual-energy multidetector computed tomography system. The left main coronary artery had a diameter of 2.5 mm (Z index of 0.55) at its origin and the presence of a saccular aneurysm with a diameter of 4.6 mm (Z index of 5.8) before the bifurcation was noted. The anterior descending artery showed a giant fusiform aneurysm from the origin of the proximal third to the middle third, with a maximum diameter of 9.3 mm (Z index of 20.6) and a total length of 27 mm, resulting in a beaded course of the artery in the proximal and middle third; no evidence of thrombus was found within the aneurysm. There was no evidence of aneurysms in the distal third. The circumflex artery showed a fusiform aneurysm in the proximal segment measuring 3 mm in diameter (Z index of 3.2) and 10 mm in length with no evidence of thrombus within. The right coronary artery showed cardiac motion artifacts: it was dilated at its origin with a diameter of 3 mm (Z index of 2.4), and a giant fusiform aneurysm was observed in the proximal third with a diameter of 7.3 mm (Z index of 13.2) and a

Table 1. Laboratory values

Blood element	Value at admission	Value during follow-up
Hemoglobin (g/dL)	12.3	12.6
Mean corpuscular Volume (fL)	82.7	83.1
Leukocytes (mL) Neutrophils Lymphocytes Monocytes	15,100 69% 17% 9%	12,900 59% 35% 6%
Plateletrs (mL)	728,000	323,000
Mean platelet volume (fL)	6.2	6.1
Erythrocyte sedimentation rate (mm/h)	95	115
Ultra-sensitive C-reactive protein (mg/dL)	12.79	12.79
Procalcitonin (ng/mL)	0.20	NEGATIVE
Urea (mg/dL)	13	13
Uric acid (mg/dL)	1.8	1.8

length of 10 mm. Finally, a saccular aneurysm of 3.8 mm (Z index of 5.8) was observed in the middle third, while the distal third showed no evidence of aneurysms.

The patient was diagnosed with classic Kawasaki disease, as she met all the criteria for the diagnosis. After 36 h of initial therapy with IVIG and anticoagulant, a recurrence of fever was observed, for which a second dose of IVIG was administered. On day 3 of hospitalization, laboratory tests showed elevated platelets and elevated ESR, CRP, and gamma-glutamyl transferase.

The patient presented a new episode of fever 36 h after the second dose of IVIG. She showed a pressing holocranial headache that improved with acetaminophen; she had systemic arterial hypertension with a maximum of 132/90 mmHg, with a heart rate within the percentile limits. A cardiologic examination revealed a Grade I systolic murmur in the mitral valve. The electrocardiogram showed regular sinus rhythm without ST-segment abnormalities. Given this situation, anti-TNFα therapy (etanercept) and glucocorticoids were proposed to the family; they were informed of the limited experience with anti-TNFα and consented to its use. No adverse events occurred during its administration or in the following days. With this therapy, the fever disappeared for more than 72 h. The patient showed improvement in her general condition; she remained hospitalized for 13 days. On the last day of hospitalization, she remained asymptomatic with stable vital signs. A control echocardiogram was performed before discharge with no new findings. Abdominal ultrasound showed no lesions in the abdominal arteries and no changes in renal artery flow. Paraclinical studies showed normalization of CRP, elevated ESR, and normalization of liver function tests; however, the patient continued with thrombocytosis. A weekly dose of etanercept was continued for 4 weeks (0.8 mg/kg/week). At the 6-week follow-up, the patient was asymptomatic, and no new coronary lesions were detected on echocardiography.

Discussion

Kawasaki disease is the most common cause of acquired heart disease in children. Aspirin and IVIG in the acute phase have been recommended to prevent damage to medium-caliber vessels, including the coronary arteries[8]. A percentage of patients do not respond to this therapy (approximately 10-20% of cases) and are considered resistant to IVIG. For patients who do not respond satisfactorily to the first treatment scheme, a second dose of IVIG is recommended, with or without methylprednisolone administration. The mechanism by which IVIG is effective in the treatment of Kawasaki disease is unknown; the reduction in coronary damage appears to be related to the regulation of the immune system, including modulation of cytokine production, neutralization of bacterial superantigens or other etiologic agents, and suppression of endothelial cell activation. According to the 2004 American Heart Association guidelines, IVIG should be administered within the first

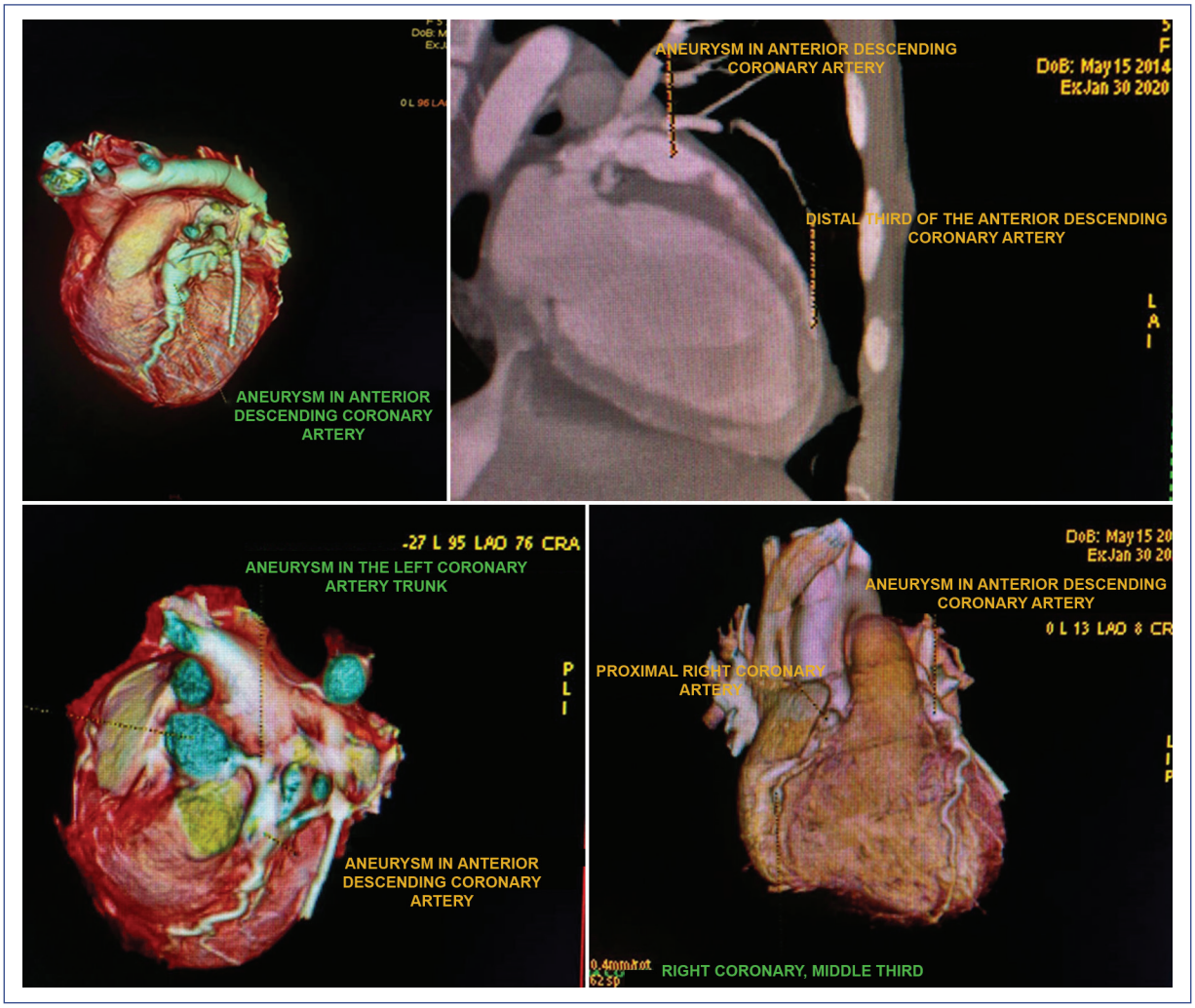

Figure 1. Angiotomographic findings. Giant fusiform aneurysms in the proximal and middle third of the anterior descending and proximal right coronary arteries. Fusiform aneurysm in the trunk of the left coronary artery and in the proximal segment of the right coronary artery. Saccular aneurysm in the middle third of the right coronary artery.

10 days (and preferably within 7 days) of disease onset. To date, the factors influencing IVIG treatment failure are unknown[9]. However, without specifying the mechanism, one study suggested that altered albumin levels may be a predictive factor for failure. Some studies have shown that early administration of IVIG (within 5 days) does not significantly improve cardiovascular outcomes but is a factor that increases the need for repeating IVIG treatment[10]. Given that an increase in TNF-α has been observed in the early stages of the disease, using blockers of this protein may modify the percentage of poor responses to initial treatment[7].

The first TNF-α antagonist monoclonal antibody used was infliximab, although the results were not convincing[11,12]. Another drug used is etanercept, which has been shown to reduce immunoglobulin resistance and prevent the appearance and progression of coronary aneurysms. However, the studies are inconclusive, probably due to the small number of patients involved[6-8].

In this case, we decided to use etanercept, considering the information on safety when administered in children with Kawasaki disease and the history of failure with infliximab[8]. The patient met the criteria for the diagnosis of classic or complete Kawasaki disease. We followed the therapeutic protocols, starting with IVIG, and after the recurrence of fever on two occasions, it was decided to provide adjuvant therapy with etanercept, indicating 0.8 mg/kg/week (12.5 mg total). A weekly dose was administered for 5 weeks. This therapeutic protocol resulted in the

cessation of febrile peaks and the stabilization of the aneurysms detected by echocardiogram and coronary angiotomography.

In Kawasaki disease, the most important factor in preventing the development of coronary aneurysms is early treatment, achieved by an early diagnosis[13]. In this case, the patient was diagnosed late (> 7 days), which increased the risk of treatment failure, especially due to coronary lesions and their progression to giant aneurysms[13]. Persistent fever in patients with Kawasaki disease, despite adequate treatment, is a sign of poor prognosis and failure to control the disease. If a second dose of IVIG has been administered, the patient is considered IVIG resistant. Given this scenario and after evaluating the reported risk-benefit ratio, we treated the patient with etanercept[5]. There is a relationship between the use of adjuvant therapy with anti-TNF-α drugs and the improvement in persistent symptoms, as well as no progression of coronary lesions. In patients with coronary aneurysms, upregulation of regulatory T cells with downregulation of activated monocytes and increased plasma concentrations of TNF-α receptors have been reported, supporting the use of blockers as adjuvant therapy[12].

Etanercept may promote earlier resolution of arterial dilation. However, the results of clinical trials under development must be evaluated before a firm recommendation for using TNF-α blockers can be made[14].

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The authors declare no conflicts of interest.

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