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(CASE REPORT)

Approach to resistant IVIG Kawasaki disease in children

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Abstract

Kawasaki disease (KD) is an acute febrile illness of early childhood characterized by vasculitis of the medium-sized arteries. There is no diagnostic test for KD because the cause is unknown, so diagnosis relies on the recognition of the diagnostic clinical criteria. The most feared sequela of KD is development of coronary artery abnormalities, which occur in 20-25% of untreated children. IVIG reduces this risk in 2-5% when administrated within 10 days from the onset of fever. Here is reported the case of an infant which resulted resistant to 2 consecutive doses of IVIG. Glucocorticoids are recommended as an appropriate therapy in IVIG resistant Kawasaki disease.

Keywords: Kawasaki disease; IVIG; Glucocorticoids; Resistance; Children

1. Introduction

Kawasaki disease (KD) is an acute febrile illness of early childhood characterized by vasculitis of the medium-sized arteries. It is rare in children older than 8-years or younger than 6-months of age, however it may occur in any age group and in adults as well. The japan doctor Tomisaku Kawasaki saw the first case, a 4-year old child with rash and fever, in 1961 at Red Cross Hospital in Tokyo. However only after 7 years he published his firs report with 50 children presented with fever, rash, conjunctival injection, cervical lymphadenopathy, inflammation of the lips and oral cavity, and erythema and edema of the hands and feet [1]. Initially it was believed that the clinical syndrome was benign, self-limited, without sequelae, when a pathologist, Noboru Tanaka discovered coronary artery thrombosis during an autopsy on a child who was previously diagnosed with the disorder. Meanwhile a pediatrician, Takajiro Yamamoto, noted that one of his patients with Kawasaki disease had a gallop rhythm associated with congestive heart failure [2]. In continuity he detected that nearly half of his patients with Kawasaki disease had abnormalities on electrocardiogram. In 1970 was published the first Japanese nationwide survey, which documented 10 autopsy cases of sudden death resulting from complications of coronary artery aneurysms after Kawasaki disease [3]. In 1976, Melish first reported Kawasaki disease in the United States, in a group of 12 children from Honolulu [4]. The disease is now recognized to occur worldwide, although the greatest number of cases has been in Japan.

Even after 6-decades of its recognition the etiology of Kawasaki disease remains unknown. Clinical and epidemiological features strongly support an infectious cause such as the incidence in the toddler age-group and the occurrence of epidemics primarily in late winter and spring. Furthermore many of the clinical features are similar to those of other infectious diseases, as adenovirus infection and scarlet fever. The findings that Kawasaki disease is rare in infants younger than 3- months of age and in adults, suggests a role of trans-placental antibodies conferring protection and that the development of protective immunity is a result of asymptomatic infection in most individuals. A genetic influence on disease susceptibility is suspected because Kawasaki disease is more frequently represented among Asian

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and Asian-American populations and siblings of affected children have a 10-20 times higher probability of developing Kawasaki disease than the general population [5, 6].

Kawasaki disease causes inflammation most prominently in the coronary vessels, however vasculitis can also occur in veins, capillaries, small arterioles, and larger arteries. In the earliest stages of the disease, the endothelial cells and the vascular media become edematous, but the internal elastic lamina remains intact. An influx of neutrophils occurs 7-9 days after the onset of fever, which is quickly followed by a proliferation of $CD8^+$ cytotoxic lymphocytes and immunoglobulin A–producing plasma cells. The inflammatory cells secrete various cytokines such as: tumor necrosis factor, vascular endothelial growth factor, monocyte chemotactic and activating factor, interleukins (IL-1, IL-4, IL-6), and matrix metalloproteinases that target the endothelial cells and result in a cascade of events that lead to fragmentation of the internal elastic lamina and vascular damage [7,8]. In severely affected vessels, the media develops inflammation with necrosis of smooth muscle cells, consequently the internal and external elastic laminae can split, leading to aneurysms. Following the next few weeks, the active inflammatory cells are replaced by fibroblasts and monocytes, and fibrous connective tissue begins to form within the vessel wall. This process inflicts the proliferation and thickening of the intima, so the vessel wall eventually becomes narrowed or occluded owing to stenosis or a thrombus. Death may occur from a myocardial infarction secondary to thrombosis of a coronary aneurysm or from rupture of a large coronary aneurysm. The risk of death is more prominent during the period when vascular damage is associated with a concomitant increase in the serum platelet count [9,10, 11].

Here is reported the case of infant with Kawasaki disease which resulted resistant to two consecutive doses of IVIG treatment.

2. Case report

A 20-months old boy admitted to the University Hospital Center of Tirana with a history of a 5-days high fever and a wide spread rash. He had taken antibiotics for the last 2 days, but the fever remained unresponsive and on the fifth day a rash spread over the body. He had no family history with SARS CoV-2 infection.

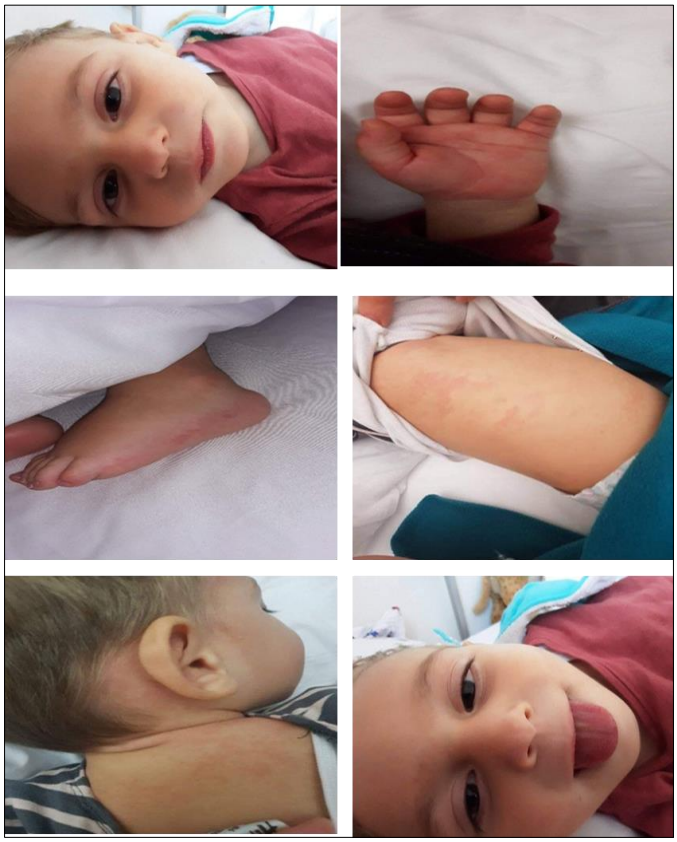

Figure 1 The child with Kawasaki disease

On physical examination he appeared ill, irritated, with high fever 40˚C and poor feeding. There were observed red cracked lips, strawberry tongue, hyperemic tonsils, and injected sclera with palpebral edema. No enlarged cervical glands were found on examination. The rash was poly-morph and spread all over the body including palms and soles. Both extremities hands and feet were swollen, indurated and slightly painful (Fig.1). The heart and lungs were normal in examination, abdomen was soft and palpable.

Tests for COVID-19 both pharyngeal RT-PCR and serology were negative. Laboratory investigations on admission revealed a blood cell count of high WBC 19,000 cells/mm3 (69% neutrophils and 24.1% lymphocytes), RBC 4,160,000 cells/mm3, Hemoglobin level 11.3 g/dL, Hematocrit value 35.7%, normal Platelet count 212,000 cells/mm3, Erythrocyte sedimentation rate 28 mm/h (<15 mm/h), normal Aspartate aminotransferase 35 U/L (14 - 35 U/L), and Alanine aminotransferase 30 U/L (9 - 24 U/L), Creatine kinase 75 U/L (30 - 200 U/L), normal Blood urea nitrogen 24.9 mg/dL (15 - 36 mg/dL), and Creatinine 0.43 mg/dL (0.44 - 0.64 mg/dL), low serum total protein 5.5 g/dL (6 - 8 g/dL), low serum Albumin 2.8 g/dL (3.2 - 4.5 g/dL), high C reactive protein 5.15 mg/dL (<0.5 mg/dL), normal D-dimer 130 mg/dL (<198 mg/dL), high Fibrinogen activity 564 mg/dL (160 - 390 mg/dL), PT quick time 101% (70% - 110%), Prothrombin time/international normalized ratio (INR) 0.86 (0.85 - 1.15), aPTT 25.7 sec (24 - 35 sec), normal Ferritin 33.00 ng/mL (5.3 - 99.9).Tab.1 Blood and urine cultures were negative. Radiologic examination of the lungs and heart were normal.

Table 1 Laboratory examination values

White blood cells	19,000 cells/mm³
Red blood cells	4,160,000 cells/mm³
Hemoglobin	11.3 g/dL
Platelets	212,000 cells/mm³
Erythrocyte sedimentation rate	28 mm/h
Aspartate aminotransferase	35 U/L
Alanine aminotransferase	30 U/L
Creatine kinase	75 U/L
Blood urea nitrogen	24.9 mg/dL
Creatinine	0.43 mg/dL
Total protein	5.5 g/dL
Albumin	2.8 g/dL
C reactive protein	5.15 mg/dL
D-dimer	130 mg/dL
Fibrinogen	564 mg/dL
PT quick time	101%
Prothrombin time/international normalized ratio (INR)	0.86
aPTT	25.7 sec
Ferritin	33.00 ng/mL

Treatment for Kawasaki disease was initiated. Medication consisted of intravenous ceftriaxone, IVIG 2 mg/kg in one admission, high dose of aspirin. Fever, rash, edema and conjunctivitis persisted after the first dose of IVIG although there was an improvement in the general condition of the child, so after 72 hours the second dose of IVIG was administrated. Fever, rash and conjunctivitis resisted to the second dose of IVIG, so intravenous corticosteroids were initiated. Fever subsided on the second day of corticosteroid administration, rash faded, conjunctivitis was no longer visible and the child was feeling well. Platelets peaked in the third week 1,750,000 cells/mm3 and a periungual desquamation of the

toes was visible (Fig.2). Platelets normalized gradually in the following weeks, and the follow up of the coronary artery resulted normal (Tab.2).

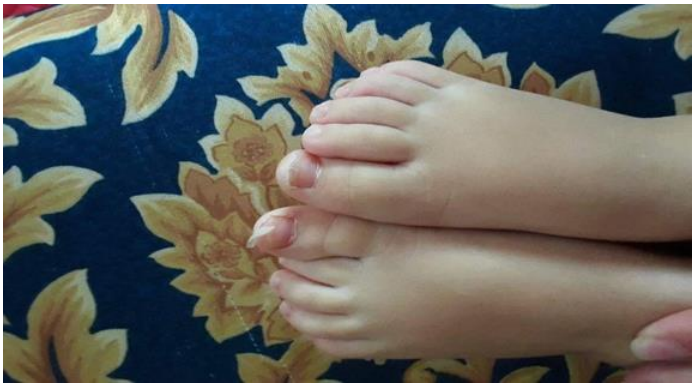

Figure 2 Periungual descuamation in Kawasaki Disease

Table 2 Clinical outcome of the patient

Hospitalization time	**1 week**	**2 week**	**3 week**	**4 week**
WBC	19,000 cells/mm^3	15,000 cells/mm^3	10,200 cells/mm^3	7,800 cells/mm^3
RBC	4,160,000 cells/mm^3	3,750,000 cells/mm^3	3,900,000 cells/mm^3	4,200,000 cells/mm^3
Hb	11.3 g/dL	10.1 g/dL	10.5 g/dL	12.1 g/dL
PLT	212,000 cells/mm^3	850,000 cells/mm^3	1,750,000 cells/mm^3	450,000 cells/mm^3
ESR	28 mm/h	25mm/h	22mm/h	15mm/h
Total protein	5.5 g/dL	6.0 g/dL	6.8 g/dL	7.4 g/dL
Albumin	2.8 g/dL	3.0 g/dL	3.2 g/dL	4.5 g/dL
C reactive protein	5.15 mg/dL	1.15 mg/dL	0.5 mg/dL	0.15 mg/dL
Fibrinogen	564 mg/dL	500 mg/dL	450 mg/dL	275 mg/dL

3. Discussion

Kawasaki disease is the leading cause of acquired heart disease in developed countries and is gradually surpassing rheumatic heart disease in developing countries. Data published from the Japanese Kawasaki disease nationwide survey reported an increased rate from 218.6/100,000 children in 2008 to 243.1/100,000 in 2011 and 330.2/100,000 children in 2015 [12,13]. In the United States, the incidence is relatively stable, the Kawasaki disease associated hospitalization rate for children younger than 5-years of age varies between 18-20/100,000 children [14]. The annual incidence of Kawasaki disease in northern and western European countries is about 10–15/100,000 children under 5 years old and seems to be relatively stable over time and space. The incidence seems to be similar in Eastern Europe, despite the limited data [15]. There are not published data of the incidence of Kawasaki disease in Albania, however it is expected to be the same as the other regions of the Europe. There is no diagnostic test for KD because the cause is unknown, so diagnosis relies on the recognition of the diagnostic criteria for KD (Table 3). A patient fulfills clinical criteria for KD if a fever is present for at least five days, if at least four of the other five clinical features are present, and the illness is not explained by another disease.

A patient fulfills clinical criteria for KD if a fever is present for at least five days, if at least four of the other five clinical features are present, and the illness is not explained by another disease. Fever marks the onset of the disease. It is remittent in nature, often 40°C or higher, unresponsive to antibiotics and partially responds to antipyretics. In untreated children fever lasts on average 10 days, but may range from 5 to 25 days. The other diagnostic criteria usually appear over the next two to five days, following the onset of fever, and typically last 10 to 14 days without treatment.

Oropharyngeal changes occur in almost all patients with typical disease and include bright red, cracked lips with generalized erythema of the oropharynx, including the buccal mucosa, and often a strawberry tongue. Most of the patients have a rash, which may have any appearance, but is rarely vesicular or pustular. Diffuse erythema in the perineal area that peels during the acute phase is seen in up to one-half of patients. Bilateral, non-purulent conjunctival injection, primarily affecting the bulbar rather than palpebral conjunctiva, occurs in 90% of patients. Most patients also have edema of the hands and feet, often with redness of the palms and soles. Cervical adenopathy measuring at least 1.5 cm is the least common manifestation, occurring in approximately 50% of patients [16,17,18]. The presented child had intermittent high fever, unresponsive to antibiotics, for 5 days and 4 from the other 5 clinical criteria (bilateral conjunctivitis, oropharyngeal changes, peripheral extremity changes and skin rash). However in many cases, the clinical criteria for Kawasaki disease may not all be present simultaneously. In such cases a careful review may reveal that one or more clinical features were present and resolved prior to presentation.

Table 3 Diagnostic criteria for Kawasaki disease

Clinical criteria for Kawasaki disease
Fever for five or more days, plus four of the following:
_ Bilateral nonpurulent conjunctivitis
_ Oral mucosal changes: red cracked lips, strawberry tongue, injected oropharyngeal mucosa
_ Peripheral extremity changes: red palms or soles, indurative edema of hands or feet, periungual desquamation in the subacute phase
_ Polymorphous rash
_ Cervical lymphadenopathy (more than 1.5 cm)

Treatment of Kawasaki disease in the acute phase is aimed in reducing the inflammation in the coronary artery wall and preventing coronary thrombosis and aneurysms. Aspirin has been used to reduce inflammation and to inhibit platelet aggregation in children with Kawasaki disease, but it does not seem to decrease the number of patients who develop coronary abnormalities [19]. High doses of aspirin (80-100mg/kg daily divided into four doses) are used during the acute inflammatory stage of the disease. The antiplatelet dose (3-5mg/kg mono dose) is continued until the patient shows no evidence of coronary changes within six to eight weeks after the onset of illness. It has been four decades till now that the efficacy of IVIG administered in the acute phase of Kawasaki disease by reducing the prevalence of coronary artery abnormalities has been well documented. So the risk of developing coronary aneurysms declined from 15-25% without treatment to 3-5% with treatment [20,21]. The mechanism of action of IVIG remains unknown, although theories include cross-linking of the Fc II and Fc γ III receptors on macrophages, induction of the immune inhibitory receptors, blocking of the interaction between endothelial cells and natural killer cells, augmenting the T-cell suppressor activity, suppression of antibody synthesis, neutralization of bacterial superantigens or other etiologic agents, and provision of the anti-idiotypic antibodies. In vitro findings suggest that IVIG blocks endothelial-cell proliferation and the synthesis of adhesion molecules, chemokines, and cytokines [21]. A single dose of 2g/kg IVIG infused over 10-12 h is the current standard of therapy. Studies documented that peak serum IgG levels were lower among patients who subsequently developed coronary artery abnormalities and were inversely related to fever duration and laboratory parameters of acute inflammation [22]. This therapy should be initiated within the first ten days of illness and when possible within seven days. The benefits of starting treatment for Kawasaki disease prior to the fifth day of illness is controversial. Any child with Kawasaki disease who has evidence of persisting inflammation, including fever or high concentrations of inflammatory markers with or without coronary artery abnormalities, should be treated even if the diagnosis is made after the tenth day of illness

As the diagnosis of Kawasaki disease was established in the presented child, treatment with high dose Aspirin and 2g/kg IVIG was initiated on the sixth day of the disease. However after 36 hours fever still persisted in lower degree (38.5-39°C) and the clinical stigmata were present too. The institution of the second dose of IVIG contemporary with prednisolone 2mg/kg resulted in resolution of fever and clinical manifestations. Ten to fifteen percent of the children diagnosed with Kawasaki disease who are treated with high-dose aspirin and 2g/kg IVIG will have a persistent or recrudescent fever. Many studies have shown that children who do not become afebrile after the first dose of IVIG are

at an increased risk of developing coronary artery aneurysms. Failure to respond is usually defined as a persistent or recrudescent fever 36 hours after the completion of the initial IVIG infusion. Most experts recommend retreatment with a second dose of IVIG, however a small group of patients fail to respond even to the second dose of IVIG. Corticosteroids also have been used to treat patients who have failed to respond to the initial therapy for Kawasaki disease [23,24].

The role of glucocorticoids in the treatment of Kawasaki disease remains controversial, although their use is the treatment of choice in other forms of vasculitis. Corticosteroids were used as the initial therapy for Kawasaki disease long before the first report of IVIG efficacy in 1984 [25]. Different studies showed that patients who received steroids had a shorter duration of fever and shorter hospital stays, as well as a lower mean ESR and median CRP six weeks after the onset of illness [26,27]. No differences between treatment groups in coronary outcomes were noted, with limited statistical power. Children, to whom corticosteroids and IVIG were administered, compared with those who received IVIG alone, had reduced levels of cytokines, including IL-2, IL-6, IL-8, and IL-10 within 24 hours of IVIG administration [28].

Other treatments successfully used in children include a monoclonal antibody against TNF- (infliximab), ulinastatin, plasmapheresis, and cytotoxic agents such as cyclophosphamide and cyclosporine A [29,30,31]. Methotrexate (MTX), a dihydrofolate reductase inhibitor, has been used for its anti-inflammatory properties in several vasculitis, and was reported to be effective in patients who are refractory to IVIG [32].

Treatment of children in which IVIG fails after the first and/or second dose remains controversial and is variable across institutions. Guidelines from the American Heart Association recommend a second dose of IVIG, glucocorticoids (methylprednisolone, prednisolone or prednisone), or infliximab to be considered for patients resistant to IVIG [33]. Cyclosporine and other cytotoxic agents, immunomodulatory monoclonal antibody therapy, and plasma exchange be reserved for exceptional patients with particularly refractory Kawasaki disease.

4. Conclusion

Coronary artery aneurysm is the most feared sequel of the vasculitis in Kawasaki disease which occur in 20-25% of untreated children. Treatment with high dose IVIG regimen within 10 days of illness reduce it in 5%. Till 10-15% of children with Kawasaki disease fail to respond to this treatment. The most recommended approach to this situation is the application of a second dose of IVIG combined with the use of glucocorticoids.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed Consent was taken from the parents of hospitalized child, reported in the study, for using the data of the medical records, and photos, providing anonymity.

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