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Mini Review

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Refractory Kawasaki disease: unusual presentation and mini review

Abstract

Kawasaki disease was first described about 50 years earlier as a systemic vasculitis; now it is the most common cause of acquired heart disease in childhood. It remains an area of controversy in regards to diagnostic criteria and treatment.

Three types of Kawasaki disease were described according to its clinical course and response to treatment. Researchers have been actively working on developing biomarkers, some of which reached the level of clinical significance which is expected to be trustful and commercially available. It is estimated that such biomarkers soon will be the corner stone in the early diagnosis of Kawasaki disease.

Pathophysiology of Kawasaki disease still not completely explored, but most researches proved that it is a super antigen disorder.

Keywords: Kawasaki, super antigen; biomarker, atypical Kawasaki, refractory Kawasaki, coronary artery lesion

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Abbreviations: KD, Kawasaki disease; SAG, super antigen; ALT, amino transferase; WBC, white blood cells; ESR, erythrocytes sedimentation rate; IVIG, intravenous immunoglobulin; IRKD, refractory Kawasaki; CAL, coronary artery lesions

Introduction

Since 1967 when Dr. Tomisaku Kawasaki first described Kawasaki disease (KD) as systemic vasculitis, there has been great efforts to identify its etiology, risk factors, clinical presentation, clinical course, long term prognosis, investigations, and effective management.

3 types of KD have been described, many risk factors were identified. Exact causative super antigens were successfully isolated and strongly linked to its etiology.

Recently; new biomarkers proved their sensitivity and specificity for early diagnosis; and new treatment modalities are being evaluated for refractory cases other than immunoglobulins. Early indicators for long term prognosis have been specified and proved trustful. In spite of all that the Best prognostic factor remains early diagnosis and proper treatment.

We present a rare case of Kawasaki disease with extraordinary long lasting and frustrating course. Despite early diagnosis and suitable treatment, this case went in a completely unexpected course .This kind of waving and long lasting course supports the super antigen (SAG) induced vasculitis mechanism and sheds light on the critical need for biomarkers which are sensitive and specific enough for early diagnosis and follow up of treatment.

Case presentation

9months old male infant presented with sudden onset of fever, anorexia and irritability for 4 days followed by nonspecific diffuse erythematous rash involving his limbs, trunk and face.

He visited the emergency department at day 2, received cefixime 10mg\kg oral once daily and paracetamol 15mg\kg, with working diagnosis of Acute Upper Respiratory Tract infection.

Laboratory results at day 2 showed: White Blood Cells (WBCs): 8k/ul (Normal range: 5-15k/ul); Neutrophils: 4.5k/ul (Normal range: 1.5-6k/ul); Lymphocytes: 3k/ul (Normal range: 5-9k/ul); Hemoglobin: 12g/dl (Normal range: 10.5-14g/dl); Platelets: 250k/ul (Normal range: 150-400k/ul); Erythrocytes Sedimentation Rate (ESR): 15mm (Normal range: <15mm/l) & C-reactive Protein (CRP): 6mg/l (Normal range: <5mg/l).

Physical Examination showed a toxic irritable baby boy, febrile (39.5°C) with red swollen digits in both hands and feet, red lips without cracking, red congested bulbar conjunctiva without discharge (Figure 1), diffuse non specific polymorphic erythematous rash on his trunk and all limbs (Figure 2) (Figure 3). No lymphadenopathy, no organomegaly and no meningeal signs.

Laboratory results at day 5 showed: WBCs: 16k/ul; Neutrophils: 14k/ul; Hemoglobin: 10.5g/dl; Platelets: 300k/ul.CRP: 98mg/l. Alanine Amino Transferase (ALT): 110IU/L (Normal range: <41IU/L). Negative Widal test, Brucella titer and normal Kidney Function tests. Cerebrospinal fluid analysis revealed normal chemistry and cytology. All cultures (Blood, Urine, Stool & CSF that were extracted at day 2 showed no growth and his Chest X ray was clear.

At day 5 clinical diagnosis of KD was made and intravenous immunoglobulin (IVIG) 2g/kg was started. Twelve hours after infusion he showed dramatic response with resolution of his rash, fever, and edema. He started to smile and ask for food. At day7, Echocardiography and abdominal ultrasound were normal. He was discharged home symptom free without medication.

3days later (10 days from initial presentation), fever returned very high up to 40°C. His physical examination revealed a febrile toxic baby with red swollen lips and digits, cracked lips with fine scales on finger tips (Figure 4). Laboratory results revealed: WBCs: 19k/ul; Neutrophils: 15k/ul; Platelets: 550k/ul. CRP: 160 mg/l & ALT: 140 IU/L. Echocardiography at day 12 revealed inflammatory changes in all coronary arteries without dilatations. Abdominal ultrasound and chest X-ray were normal.

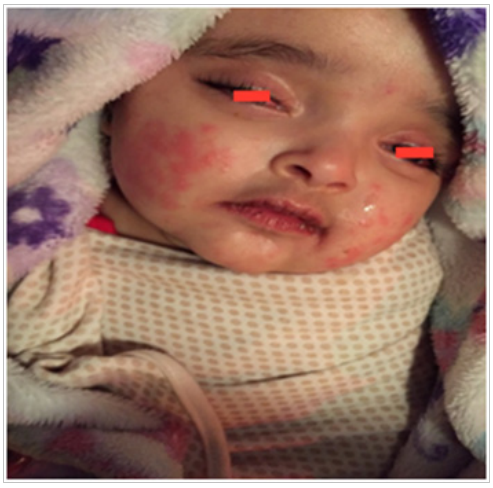

Figure 1 Non secretory conjunctivitis and facial erythema.

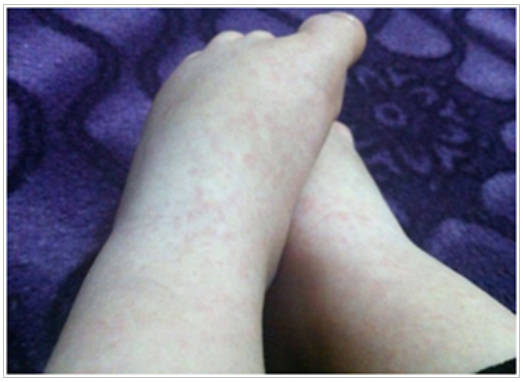

Figure 2 Non vesicular popular erythematous rash on legs and feet.

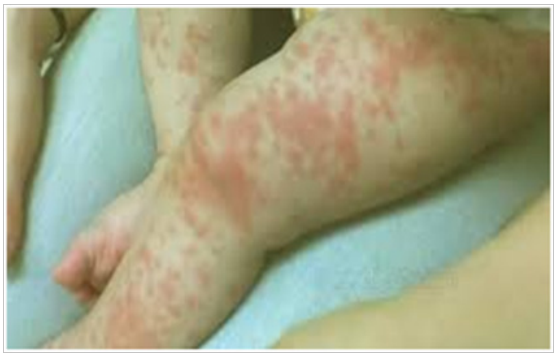

Figure 3 Diffuse polymorphic erythematous rash on lower limbs and trunk.

The case was diagnosed as "Refractory KD or IVIG-Resistant KD". Second dose of IVIG 2g/kg was given and Aspirin 40mg/kg/day orally were initiated. He responded properly with almost complete resolution of signs and symptoms within 24 hours. At day 15 laboratory results showed: WBCs: 8k/ul; Neutrophils: 3k/ul; Hemoglobin: 9.3g/dl; Platelets: 250k/ul; CRP: 16mg/l &ALT: 50IU/L. He was discharged home on Aspirin 40 mg/kg and omeprazole 2mg/kg.

Unfortunately, only 2 days later (day 17), hyperpyrexia up to 41°C bounced back and he was readmitted .Full septic screen showed no clear etiology of fever at day 20. High dose of Methyl prednisolone 30mg/kg/day for 3 days was started. From the first day he responded with complete absence of fever. However 3 days of bolus steroid was recommended by the pediatric rheumatologist.

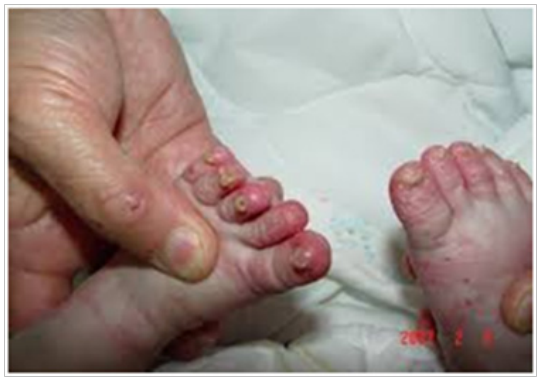

Figure 4 Red swollen digits with scales, nail fissuring and cracks.

After those 3 days everything returned normal and he was about to be sent home when fever spiked again, with obvious reappearing of the polymorphous rash on trunk and limbs in addition to edema in digits and nails cracking and lysis. Rheumatologist advised to start Infliximab in addition to methyl prednisolone to avoid further deterioration due to the risk of toxic shock like syndrome which may cause multiple organ failure.

Second shot of methyl prednisolone was started while his transfer to the pediatric rheumatology unit be arranged. After 3days transfer arranged, but his parents asked for discharge on their own responsibility as he became completely symptom free. Although there was a high risk that he may relapse as usual; he left the hospital on aspirin 5mg/kg/day.

7days later, a call with his family was reassuring and he was still symptom free. One month later, he came for follow up, healthy, symptom free, all his laboratory results were normal. Echocardiography was stable without aneurysm formation.6months later his echocardiography normal, with complete recovery.

Discussion

Three clinical types of Kawasaki have been described, typical, atypical and refractory Kawasaki disease. Typical KD can be diagnosed clinically when fever for 5days in addition to 4 from the 5 major criteria: Lymphadenitis, Conjunctivitis, Polymorphous rash, Oral mucus membranes changes and Swelling or redness in extremities. No laboratory findings are of diagnostic significance. These major criteria may not be found at the same time, butthey occur in sequence.

Atypical KD can be diagnosed clinically when fever and at least 2out of5 major criteria should be present. It is most common in male infants younger than one year, and the risk for Coronary artery lesions (CAL) is as high as typical KD. The presence of the following findings aid the diagnosis: High CRP, High ESR, Thrombocytosis, Hyponatremia, Anemia and High ALT. However, the presence of the following findings excludes the diagnosis: Tonsillitis, Secretory conjunctivitis, Isolated intra-oral ulcers, Bolus rash and generalized lymphadenopathy. When atypical KD is highly suspected IVIG should be started and treated as typical KD.[1,2]

Refractory KD: persistence or relapse of fever from 36hoursup to 2 weeks after the IVIG infusion, without clear focus of infection or clear etiology is enough to diagnose refractory Kawasaki (IRKD).

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Risk factors for refractory KD are: Young age, Male gender, PLT<300,000 at diagnosis, High CRP, High ALT, Hyponatremia, and Hypoalbuminemia. Refractory KD has higher risk of coronary artery lesions (CAL).[2]

KD is one of the most common vasculitides of childhood .incidence in children under 5 is higher than what it was thought, about 5.5/100000 in UK,[3] up to 25/100000 in India, south Asia and japan according to ethnic origin more than to geographical location.[1,3] The highest incidence as high as 1% is in Japanese boys from 6-12 months of age.[4,5] Incidence is 10 folds higher for children with affected siblings.[4]

Without treatment, acute inflammation and fever disappear within 12 days, but unfortunately 20% of those patients who are not treated in the early phase develop coronary artery lesion (CAL). CAL cannot be detected by echocardiography before day 7 of fever. Early administration of IVIG within 10 days reduces the prevalence of CAL five folds to<4%. 10-15% of KD are resistant to IVIG and the longer the duration of fever the higher the risk of CAL. Echocardiography should be done every week during the first month every month for 3 month then every 3 months for 12 months.

Treatment of KD

According to the recent guidelines 40mg/kg Aspirin is as effective as the high dose of 80 mg/kg that recommended by the American Heart Association to treat Kawasaki. Aspirin only decreases inflammation, but has no effect on the prevalence of CAL or its progress, therefore it is optional to give high or low dose, if the case treated early with IVIG and responded properly with no evidence of CAL by echocardiography, it is possible not to give aspirin.

For IRKD guidelines from the American Heart Association, Centre of disease Control and Up-to-date indicate second round of high dose IVIG to be given when other clear etiologies of fever have been excluded. Aspirin 40 mg/kg for 2 weeks or for 3 days after resolution of fever is indicated too. Aspirin should be continued in a small anticoagulant dose 5mg/kg, enough to disturb the platelets cyclic oxygenase enzyme, for at least 2 months if no CAL disclosed, or till complete resolution of CAL if present.

For Resistant IRKD, after 2nd dose of IVIG, it is of no benefit to give extra doses of IVIG, and it could be harmful. Best treatment is to give single dose of IV Methylprednisolone (30mg/kg) as daily dose for 3 days or till the patient is a febrile. It is a waste of time and useless to give further courses of Methylprednisolone.

More advanced therapeutic choices are indicated, like IV infliximab 5mg/kg single dose .Infliximab is a humanized monoclonal anti TNF antibody, first extracted from mice. It is now used in the treatment of Crohn's disease ,ulcerative colitis ,and many other refractory rheumatology and inflammatory diseases on relatively large scale in recurrent IV infusions protocols.The efficacy of infliximab as a treatment for IRKD has been documented as high as 95 to 99%.[1,2]

Kawasaki the super antigen disease

Bacterial SAGs are potent T cell activators. In humans, they cause toxic shock syndrome and scarlet fever, and are implicated in Kawasaki disease, autoimmunity, atopy and sepsis. It may impair host immune responses increasing bacterial carriage and transmission. SAG causes polyclonal T cell activation and produce non-Ag specific regulatory T cells. These cells increase CTLA-4 and CD127 expression and exhibit functional suppressor activity comparable to natural T regulators. This provides a mechanism for bacterial evasion of immune response through the super antigen induction of T regulators.[6]

SAGs like TSST1 and SPE (A,B) have been isolated from different anatomical sites in KD patients. Staph and streptococcus colonizing the gastrointestinal tract produce these super antigens which are absorbed by mucosa and stimulate local and systemic T cells.[7] High release of IL6 & IL10 & GM-CSF causes vascular endothelial damage. This will facilitate infiltration of active CD4 and CD3, Monocytes and Macrophages into vascular wall causing Vasculitis.[4,8]

Investigators demonstrated high levels of IL6 and GM-CSF in KD patients and high level of TCR-VB2 bearing T cells in their peripheral blood during acute phase and it decreased during convalescence.[4,7] T cell regulatory protein inhibitor which controls the triggering of TCR-VB2 may be absent or malfunctioned due to a gene mutation.[5]

Staph aureus and streptococcus pyogenes produce super antigens that can cause Vasculitis.[3] Yersinia psudo tuberculosis is the only gram negative bacteria that can produce super antigen and it can cause Kawasaki like Vasculitis.[9] Kawasaki disease occurs in outbreaks and shows seasonal variation (highest in early spring).[1,2] It affects siblings at the same family 10 folds higher with the second sibling always affected within one week period.[9,4]

Antigen and SAG

Antigens need suitable intracellular processing in Macrophages through 2 pathways

MHC-CLASS1, OR MHC-CLASS2 pathways during that the antigenic molecule is isolated and bound to the MHC complex and present to the outer cell membrane properly to stimulate T cell helper and regulator at the same time in order to enhance immunologic response specific to this antigen and keep the inflammatory response under control.[7]

SAGs are medium sized proteins that can bypass the conventional antigen processing to bind directly to the TCR-V receptor variable segment in site beta2 forming trimoleculer complex with MHC-2. This causes polyclonal T cell proliferation and massive release of cytokines, interleukins, and TNF. But this massive immune response is not specific is not specific to the SAG. Also high ILs titer will impair the normal T cell function and help the invading pathogen to evade the immune response.[6,9]

Types of SAGs

Bacterial SAGs: 41 bacterial SAGs have been isolated all are toxins produced intracellularly and released outside. Staph aureus alone produce 18 enterotoxins like TSST1-2, SETs, VT [9]. Streptococcus pyogenes produce 12 SPE-M has similar stricter to the cardiac cell membrane presenting antigen system in some people only by contrast, the MHC complex seems to resist the rheumatogenic effects of SPE-K and M super antigens in other individuals.[8,4] Mycoplasma produces one SAG only.

Viral SAGs

A rare type of retrovirus MMTV. Is the only known virus to produce SAG, many other viruses however, like EBV and CMV play essential role to activate human cells to produce their own destructive SAGs.

Endogenous SAGs

We usually think of super antigens as dangerous toxins that may cause toxic shock and death. Now it seems that we all have SAGs genes lying dormant and waiting to be activated.[10] First isolated endogenous SAG was the HERV-K18 which is a gene located on

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chromosome 1; named the human endogenous Retrovirus. This gene can be activated by EBV infection to produce a protein that acts as SAG. Now we know many other endogenous SAGs most important of them is the IDDMK-1 and 2.EBV virus infection can activate these genes to produce SAG that causes massive immune response and destroy the insulin producing beta cells and can cause insulin dependent diabetes mellitus.[4,10]

Filamin C and Meprin A

KD is the result of exaggerated immune response to infections. Enzyme MEPRIN-A (Endopeptidase-2) and the muscle protein FILAMIN-C concentrations were significantly elevated in urine and serum of KD patients compared with the non- KD controls. Levels of both biomarkers decreased to normal after IVIG treatment; this was recently described by a research group at Harvard Medical School with persistence of high levels after treatment seen in cases of resistant to IVIG and in cases of persistence of the active disease.

Enzyme linked immunosorbent assay for these 2KD specific proteins in urine has been developed and soon will become routinely available to diagnose this life threatening vasculitis early, and to follow resistant cases.[11]

CXCL10(IP)

Study on 214 children with suggestive KD done in Japan to find unique proteomic biomarker that can be used to facilitate earlier diagnosis of KD. They found that the level of CXCL10 (IP10). Is elevated in almost all patients, and it returned to normal after IVIG treatment. The confidence interval was 95%, sensitivity 100% and specificity 77%. It is a good predictor for KD and may be used as a biomarker to facilitate the diagnosis. CXCL10 is a protein produced by monocytes, endothelial cells, and fibroblasts as a response to gamma interferon. That is why it is called the Interferon Gamma Induced protein 10(IP10). It acts as a small chemokine to attract macrophages and T cells and Natural killer cells.[12]

Conclusion

KD is the result of exaggerated immune response. Mostly via the SAG pathogenesis. It is the most common cause of acquired heart disease in children. All patients have cardiac involvement ranging from mild endocarditis to lethal pancarditis. CAL is the main cause of mortality and long term morbidity. Diagnosis of KD is mainly clinical. However, specific biomarkers have been developed and trusted.

Atypical Kawasaki and refractory cases has been increasingly diagnosed. KD should be kept in mind in each infant or toddler who has nonspecific fever and rash. IVIG should be started once the diagnosis is highly suspected clinically. Early treatment is best way to control coronary vasculitis. Even after day10 IVIG still the best treatment to control the acute phase. The acute phase usually resolves within 2 weeks without treatment, but it may persist longer with persistent high fever. It is crucial to take a good history, as the criteria of Kawasaki may occur in sequence and not found at the same time.

2 bolus courses of methylprednisolone may be useful to control refractory cases before administration of infliximab in young children. However, this point needs longitudinal study and research. Biomarkers soon will be available for early diagnosis and follow up.

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Conflicts of interest

The authors declare there is no conflict of interests.

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