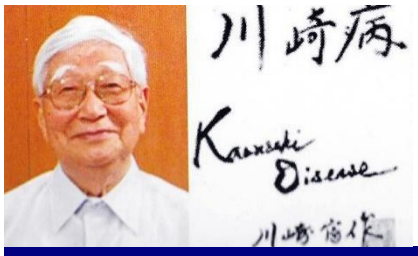

Kawasaki Disease

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1. INTRODUCTION

Kawasaki disease (KD) is an acute self-limiting systemic vasculitis of unknown origin. This was defined as mucocutaneous lymph node syndrome by Dr.Tomisaku Kawasaki in Japan and first 50 cases had been published in 1967. It has been found to be the leading cause of acquired paediatric cardiac disease worldwide, especially in developed countries (1, 2). Coronary artery lesions (CALs) with aneurysmal dilation, thrombosis, and/or stenosis, leading to myocardial infarction and death, have been recognized as the most severe complication in children (3, 4). Circulating immune complexes (ICs), triggered by infectious agents, bacteria, or viral or other unknown cause, have been detected in the early phase of KD, implicating that immunopathologic mechanisms might be involved in the pathogenesis of vasculitis in KD (5-8). Attempts to produce coronary vasculitis have been made in mice, weanling rabbits, and guinea pigs by injecting infectious agents, foreign proteins, horse serum and *Lactobacillus Casei* cell walls (9,10). Among the animal models, swine may be the unique and promising animal for biomedical research, especially in the field of cardiovascular diseases (11,12). Recent advances in genetic analysis are contributing our understanding of pathogenesis and newer modalities in management of KD.

2. EPIDEMIOLOGY

KD is more prevalent in Asian children. According to recent epidemiologic studies, Asian populations have a much higher incidence of KD (13). Seasonal variations, chronological and geographic clustering have been observed. Approximately 80-90% of patients with KD are seen below 5 years of age. **Japan** has the highest annual incidence in the world (308 per 100,000 children < 5 years of age between 2013-2014 and increased further to 330.2 in 2015, followed by **South Korea** 199.7 per 100 000 children < 5 years of age in 2014, and **Taiwan**

has the third highest 82.8 per 100 000 children <5 years of age in 2010. In Taiwan, they estimate that approximately 700 KD patients in a year are newly diagnosed. In **Hawaii**, with its complex multi-racial and multi-ethnic population overall annual incidence is about 50.4/100,000; for Japanese ethnic children in Hawaii, the rate is 210. **Beijing** has reported an increased incidence, increasing from 40.9 to 55.1 in 2004, increased to 110 (2014) per 100 000 persons. In **Shanghai** it increased from 16.2 (1997) to 71.9 (2012) per 100000 children <5 years (13-17). In **Hong Kong**, the average annual incidence was 39 per 100 000 between 1994 and 2000. In Western countries, the incidence of KD is significantly lower. **Canada** reported an annual incidence of 20.6 per 100 000 for the period between 1998 and 2007. The **United States** had an annual incidence of 17.1 per 100 000. Almost 12000 new cases are detected every year in Japan. Coronary artery lesions after 30 days of illness was seen in only 3% in Japan. Decreasing trend of coronary artery complications in Japan may be indicated that almost all KD cases had received IVIG as first line of therapy. The ratio of male and female KD patients approximates 1.5:1 in virtually all countries.

KD has striking age distribution, with almost 100% cases occurring in children, 80-90% in children <5years and 50% in those <2 years old. We must admit seriously that we do not have sufficient data to present the epidemiology in India till today except regional data from the individual medical colleges. KD incidence at **Chandigarh, North India** during 2009-2014 was 7/100,000 children below 15 years of age. The first case was diagnosed in 1994. The number of cases detected during 1994-2017 is 680 and trend showed two-fold rise of KD cases for last four years (2014-2017). Recurrent KD was 0.98% and 2% was within 10 months of first episode. Incomplete KD was more common during recurrence. (18,19) The recurrence rate is approximately 2% in Taiwan and 3.5% in Japan. The case fatality rate is <0.1% in both **Japan and Taiwan**.The peak seasons of KD are late spring and summer in Taiwan.(19)

3. ETIOPATHOGENESIS

Etiology still remains unclear. Both epidemiological and clinical features of KD strongly suggest possible infectious agents. Super-antigen (unconventional protein that leads to massive T cell activation and cytokine production) from infectious agents such as beta haemolytic streptococci can trigger the immune complex vasculitis evidenced by very high titre of ASO. Some of the implicated pathogens are staphylococcus, streptococcus, Yersina, Adenovirus, human parvovirus and herpesvirus etc. The lack of responsiveness of KD patients to antibiotic therapy makes a viral etiology more likely than bacterial. Other non-infectious triggering agents also may trigger immune complex vasculitis leading to signs and symptoms manifested in KD. Moreover, the prevalence of CD8 T cells in the inflammatory infiltrate and the upregulation of cytotoxic T cell and interferon pathway genes in the coronaries of children who have died of KD are suggestive of a possible viral etiology. Rowley and Shulman proposed possible model pathogenesis as unknown infectious agents possibly viral agent infects ciliated bronchial epithelium cells in a small subset of genetically predisposed children. Agents enter blood stream via macrophages and antigen in circulation attach B cell and mediated plasma cell and generate antibody. This results in circulating antigen -immune complexes that damages endothelium of medium and small vessels particularly coronary artery with further neutrophil mediated lysosomal enzymes, and platelet aggregation that eventually damages the vessel wall causing aneurysms. (17)

3.1 Dengue fever triggering KD

Later in the course of Dengue fever, some patients may have findings that resemble Kawasaki disease and incidence of KD after dengue fever in India, notably significant. High dengue virus load modulates human microvascular endothelial barrier function and disrupts the function of

inter endothelial junctional proteins during early infection with organ specific cytogenic production.High levels of cytokines, chemokines and adhesion molecules were differentially produced in a modelling study, potentially it can cause arteritis, including coronary arteritis, which is the hallmark of KD. (20-23)**.** Adeno virus can also trigger KD. In a monozygotic twin boy had Adeno virus type 3 infection and subsequently developedKD proved by lab investigation specific to adenovirus (24).

3.2 Environmental Factors:

Efforts to isolate the causative agents of KD, researchers focused on the microbiology of aerosols. Studies by Jane C Burns et.al on environmental trigger had opened up new light on causative agents and results suggest that the triggers for KD could be wind-borne (25). By enlarge a specific etiologic agent couldn't identify the causative agent for KD and considered as unknown to date (24). These all case reports and circulating IC isolation from the sera of KD suggest that KD is an immune complex vasculitis and further evidenced by the swine animal model in which similar manifestations reproduced by the horse serum. (11, 12)

3.4 Genetic susceptibility

Recent advanced studies on gene analysis in KD were reviewed by Kei Takahashi and team, contributing not only to prediction of disease susceptibility but also to improving our understanding of the pathogenesis of Kawasaki disease and development of new improved therapies. (26)

4. HISTOPATHOLOGY

Coronary arteritis begins 6-8 days after the onset of KD sometimes even earlier with inflammation of all layers of artery. It, begins as edematous dissociation of tunica media and

infiltration of monocytes and lymphocytes. However, many neutrophils are also seen.Periarteritis further damage elastic lamina, smooth muscle cells (SMC), leading to intense damage and dilation of the artery. Inflammatory infiltration continues till 25th day of KD, then gradually decrease in number.Myocarditis has not received much attention in KD (27). Myocarditis is a well-recognized component of Kawasaki disease, with subtle left ventricular dysfunction occurring in more than half of the patients during the acute phase of the disease. It may be transient. In KD, myocarditis develops even earlier than epicardial coronary arteritis; it peaks by disease day 10 and then disappears gradually after day 20. Inflammatory cell infiltration, consisting mainly of lobulated leucocytes and large mononuclear cells, is seen in the myocardial interstitium in all cases (27). It is well known that TNF-alpha is a key inflammatory cytokine that is initially produced by T lymphocytes, followed by a secondary TNF-alpha release from monocytes/macrophages. TNF-alpha mediates endothelial cell activation through increased expression of adhesion molecules and also upregulates expression of chemokines that are important in the orchestration of leukocyte–endothelial cell interactions. Hence role of Infliximab in treating KD is important.

5. ANIMAL MODELS IN RESEARCH

Various studies on animal models on vasculitis induced by candida albicans cell wall, lactobacillus casei, serum albumin from horse serum in murine and swine models, mimic almost all features of Kawasaki disease. These findings are consistent with the role of immune complex vasculitis in the pathogenesis. Recent publication on rabbit model of arteritis displayed histopathological and ultrastructural features similar to those of KD. (11, 12). Weanling rabbits and swine model may serve as experimental model for IC vasculitis thatmimics KD than murine model. It is speculated that circulating immune complexes, triggered by infectious agentsimplicating that immunopathologic mechanisms might be

involved in the pathogenesis of vasculitis in KD (5 – 8). Changes in the coronary arteries after immune complex vasculitis have been studied (Table 1 & Fig.1 A-D). Histopathology in human KD coronary arteritis is very much similar to immune- complex vasculitis induced by horse serum.

Table 1 . Histopathology of coronary artery in immune complex vasculitis animal model

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02-04 days

Leucocytic and lymphocytic cellular infiltrates in the myocardium, perivenular and peri-arterial infiltrates in the heart. Cellular infiltrates in the smooth muscle cells and around the vasovasorum of the aorta and in the distal tubular areas of the kidney.

05-13days

Intimal thickening, inner smooth muscle cells proliferation (Fig.1 A-B), patchy edematous changes and early SMC disorganization in coronary arteries. Cellular infiltrates were few. Iliac artery showed mild intmal thickening.

14-24 days

Intima and inner SMC proliferations, moderate to severe disorientation of SMC (Fig.1C), edematous separationof SMC (Moth eaten appearance), Subintimal changes, such as coagulation of the cytoplasm, and disorientation, separation, cytolysis, vacuolization, degranulation, collagen deposition in coronaryarteries. Intimal proliferation of intramural artery.

25-60days

Patchy areas of fibrosis within the SMC (Fig. 1D), resolving stages, No further progression of proliferation of SMC in the tunica media and intima.

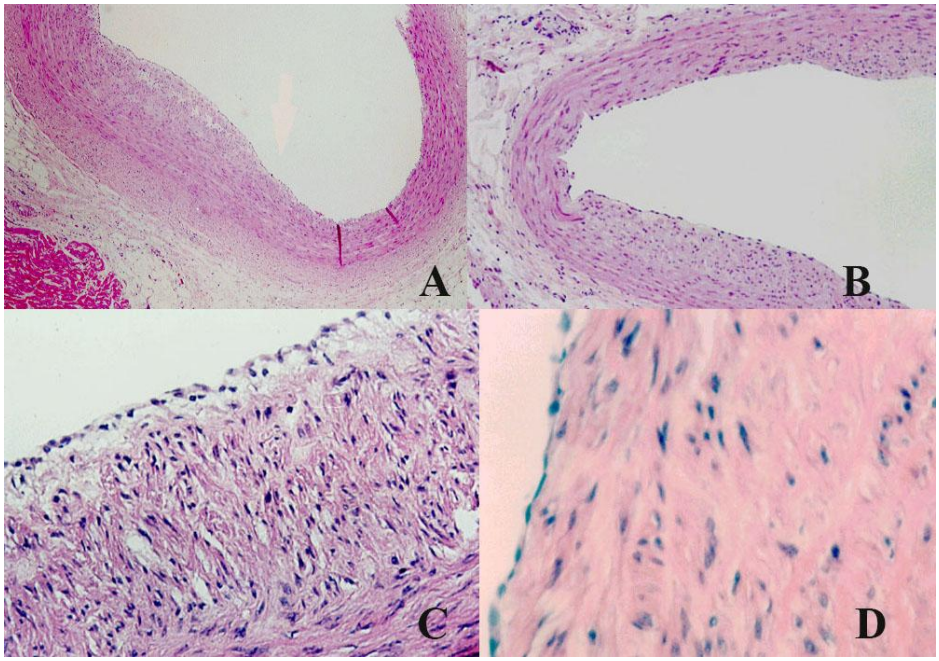

Figure 1 A-D: A-B; Left anterior coronary artery showed intimal proliferation extending to media (5-13days), C; Disorientation of smooth muscles in vertical direction (14-24 days), D; fibrosis of the arterial wall (25-60days)

6. CLINICAL SIGNS AND SYMPTOMS

Kawasaki disease is diagnosed on the basis of characteristic clinical signs and symptoms. There is no single diagnostic laboratory test.

6.1: General Feature and Diagnostic Criteria

The principal symptoms of Kawasaki disease are **fever persisting for 5 days or longer, bilateral conjunctival injection without exudate, changes in the lips and oral cavity, polymorphous exanthema, changes in the peripheral extremities and acute non purulent cervical lymphadenopathy (>1.5 cm, usually unilateral, even >1 cm in infant is significant).** At least five of those six principal signs and symptoms should be present for a diagnosis of Kawasaki disease. (29, 30) as per diagnostic Guidelines of Kawasaki Disease (MCLS: Infantile Acute Febrile Mucocutaneous Lymph Node Syndrome) adapted from

Kawasaki Disease Study Group of the Ministry of Health, Labour and Welfare Japan **(Table 2).** (29) High irritability and persisting fever in a child especially in less than 6 months of age, Erythema around the BCG scar (18-24%), perianal excoriation, 'Beaus line' on nail bed etc. are additional supporting evidence for the confirmation of KD. Eastern and northern India KD cohort had found that orange brown chromonychia is a novel finding seen in 63% of patients. (30) Asymptomatic pyuria may be associated with co incidence of severe coronary artery lesion, so it is necessary to look for the urinary pus cells and thrombocytosis or rising trend of platelet count may consider as an add on confirmatory diagnosis of KD. The only difference in AHA criteria is that fever is considered as a principal symptom and other 5 criteria was included as principal clinical findings. Few important diagnostic clues are irritability, rising trend of platelet, early periungual peeling, erythema around the BCG scar, nonexudative clean bulbar conjunctivitis, chromonychia and beaus line These signs enable further confirmation from other differential diagnosis overlapping with KD diagnosis (**Table 3, Figure 2 A-E**). Thrombocytosis and periungual peeling would be an additional clue to diagnosis of KD.All cases of suspected KD must be evaluated for incomplete subset of KD and should be treated as KD once the criteria fulfilled for incomplete KD to prevent coronary artery complications, in fact incomplete KD may more prone for developing coronary artery complications than complete KD. **(Table 4)** Other important diseases overlapping with the signs and symptoms of KD should be scrutinised for differential diagnosis (**Table 5).**

Table 2. Diagnostic Guidelines of Kawasaki Disease* (MCLS: Infantile Acute Febrile Mucocutaneous Lymph Node Syndrome) Adapted from Kawasaki Disease Study Group of the Ministry of Health, Labour and Welfare Japan.

The symptoms can be classified into two categories, principal symptoms and other significant symptoms or findings.

A. Principal symptoms

- **1. Fever persisting for 5 days or more (inclusive of those cases in whom the fever has subsided before the 5th day in response to therapy)**
- **2. Bilateral conjunctival congestion**
- **3. Changes of lips and oral cavity: Redding of lips, strawberry tongue, diffuse injection of oral and pharyngeal mucosa**
- **4. Polymorphous exanthema**
- **5. Changes of peripheral extremities:**

  (Acute phase): Reddening of palms and soles, indurative oedema

  (Convalescent phase): Membranous desquamation from fingertips
- **6. Acute non purulent cervical lymphadenopathy**
- At least five items of six should be satisfied for diagnosis of Kawasaki disease by JMC and five of six with fever should be satisfied for AHA criteria. Further one point less in JMC or 4/5 criteria considered as incomplete KD
- However, patients with four items of the principal symptoms can be diagnosed as Kawasaki disease when coronary aneurysm or dilatation is recognized by two-dimensional (2D) echocardiography or coronary angiography.

B. Other significant symptoms or findings

The following symptoms and findings should be considered in the clinical evaluation of suspected patients.

1. Cardiovascular: Auscultation (heart murmur, gallop rhythm, distant heart sounds), ECG changes (prolonged PR/QT intervals, abnormal Q wave, low-voltage QRS complexes, ST-T changes, arrhythmias), chest X-ray findings (cardiomegaly)
2. 2D echo findings (pericardial effusion, coronary aneurysms), aneurysm of peripheral arteries other than coronary (e.g., axillary), angina pectoris or myocardial infarction
3. Gastrointestinal (GI) tract: Diarrhoea, vomiting, abdominal pain, hydrops of gallbladder, paralytic ileus, mild jaundice, slight increase of serum transaminase
4. Blood: Leukocytosis with shift to the left, thrombocytosis, increased erythrocyte sedimentation rate (ESR), positive C reactive protein (CRP), hypoalbuminemia, increased α2-globulin, slight decrease in erythrocyte and haemoglobin levels
5. Urine: Proteinuria, increase of leukocytes in urine sediment
6. Skin: Redness and crust at the site of BCG inoculation, small pustules, transverse furrows of the finger nails
7. Respiratory: Cough, rhinorrhoea, abnormal shadow on chest X-ray
8. Joint: Pain, swelling
9. Neurological: Plieocytosis in cerebrospinal fluid (CSF), convulsion, unconsciousness, facial palsy, paralysis of the extremities.

***Guidelines for the Diagnosis; The difference of JMC from American Heart Association KD criteria is fever is included in the principal symptoms, whereas fever is essential to diagnose KD in AHA criteria**

Table 3. Few important striking signs in KD to confirm the diagnosis

• Irritability with fever
▪ Early peri ungual and perianal excoriation often within 10 days in the acute phase of fever
▪ Rising trend in thrombocytosis
▪ Erythema around the BCG scar
▪ Orange brown chromonychia a novel finding seen in 63%
▪ Beaus line in 3rd to 4th week
▪ Clean bulbar conjunctivitis

Table 4: Evaluation of suspected case of incomplete Kawasaki disease

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Children with fever >5days with 2 or 3 fullfilled criteria Or infants with fever >7days without explanation need laboratory test with CRP & ESR.

A. If CRP <3mg/dl &<40mm/hr, advise echocardiogram to see any coronary involvement especially peeling occur. If CA involved treat as KD.

B. If >3mg/dl/or ESR >40mm/hr , see for AHA special criteria* given below

1. **Anemia for the age**
2. **Platelet count of >450,000 after the 7th day fever**
3. **Albumin < 3g/dl**
4. **Elevated ALT level**
5. **WBC count >15000/mm ^{3}**
6. **Urine >10wbc/hpf**
7. **Or PositiveEchocardiogram**

*** 3 or > 3 Lab finding is significant and treat as KD**

Table 5. Major Differential Diagnosis

▪ **MEASLES**
▪ **SCARLET FEVER**
▪ **JUVENILE RHEUMATOID ARTHRITIS**
▪ **STEVENS-JOHNSON SYNDROME**
▪ **DRUG REACTIONS**
▪ **TOXIC SHOCK SYNDROME**
▪ **LEPTOSPIROSIS**
▪ **STAPHYLOCOCCAL SCALDED SYNDROME**
▪ **MERCURY POISONING**

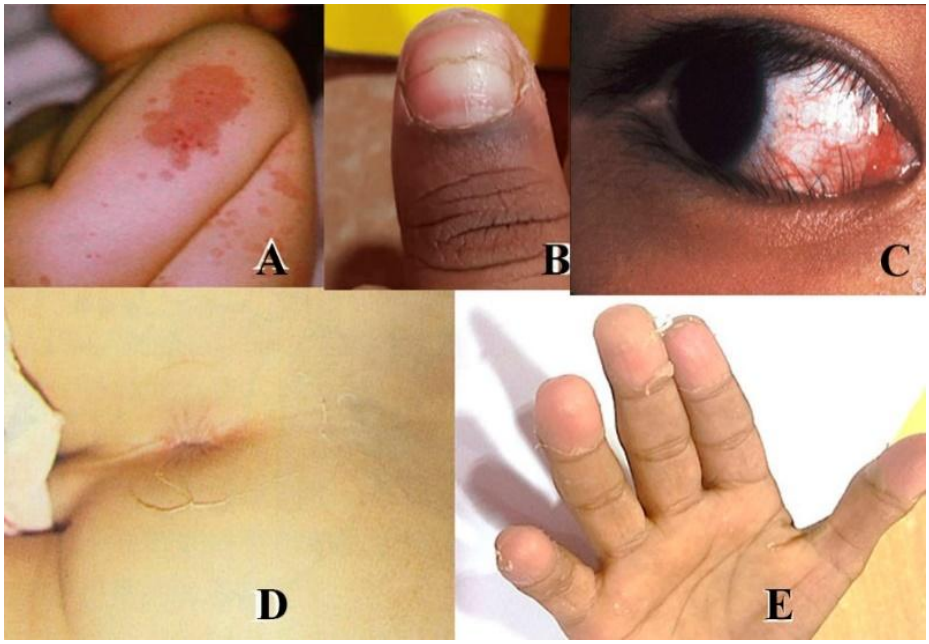

Figure 2 A-E; Erythema around the BCG scar, B; Beaus line- A transverse line or groove well seen over the thumb nail 3-4week, C; Non purulent conjunctivitis D; Perianal excoriation, E; Typical periungual desquamation

6.2 Cutaneous manifestation in Kawasaki disease

Kawasaki disease (KD) is the second common vasculitis in childhood following Henoch–Schönlein purpura. The commonest cutaneous manifestation is the rash which usually appears by the 5th febrile day. It is usually **erythematous maculo-papular** (Fig.3A) present predominantly on the trunk. However, a variety of rashes have been described: **scarlantiform, erythema multiforme like, erythroderma**; and can sometimes be pruritic. A vesico-bullous or pustular rash is not consistent with KD, but erythema nodosum, ulcerative or bullous lesion can rarely occur in association with KD. Affection of the oral mucous membrane leads to erythema, **dry fissured lips** and sometimes a **strawberry tongue**.

Extremity changes form one of the striking diagnostic features in KD. The erythema of the palms and soles together with oedema of the hands and feet which may occasionally be painful often occur in the acute phase. The other classical finding is the periungual desquamation in the fingers and toes that starts around the end of 2nd week (**Figure 2E, Fig.3 B&E**). Though a consistent clinical finding, but because of the late appearance in the subacute phase its clinical utility lies in only confirming the diagnosis retrospectively. The periungual desquamation **(Figure 2E)** is however preceded by perineal desquamation (**Figure 2D**) that may be present as early as end of 1st week. Few patients may also have peri/ supra orbital erythema followed by excoriations. Another well described albeit a bit rare sign are the transverse grooves called Beau's lines **(Figure 2B**) on the nails which may appear as late as 1 to 2 months after the disease onset. Beau's lines are better felt than visually appreciated.

An interesting finding which is almost pathognomonic of KD is reactivation of the BCG scar (Erythema around the scar may turn into ulcerative in some cases(**Fig. 2A &3C**) observed in 10-15% children. A recently described clinical finding is orange-brown chromonychia which means an abnormal reddish/ orange brown change in colour of the nail plates and / or subungual tissue. The coloured lines start appearing usually around the 5^{th} to 8^{th} day of illness, though they may be noticed as early as the 4^{th} day of fever mandating it as an early sign in the diagnosis (30). Once it appears the colouration stays unchanged over the next 7 to 10 days. Better appreciated in the fingers (Fig. 3D) than the toes, they start disappearing by the end of 2^{nd} week. Thus, on appearing they are present throughout the acute phase of illness as opposed to most of the classical clinical signs in KD which are known for their markedly temporary appearance.

Other than the chromonychia, few case reports describe some inconsistent nail changes following KD like onycholysis, onychomadesis (spontaneous separation of the nail from the matrix), spontaneously resolving pincer nail deformity (transverse curling of the nail along its longitudinal axis) and leukonychia partialis(abnormally white proximal portion of the nail) . However, all these nail abnormalities are nonspecific, maybe associated with other systemic triggers and generally resolve spontaneously within 1–2 months.

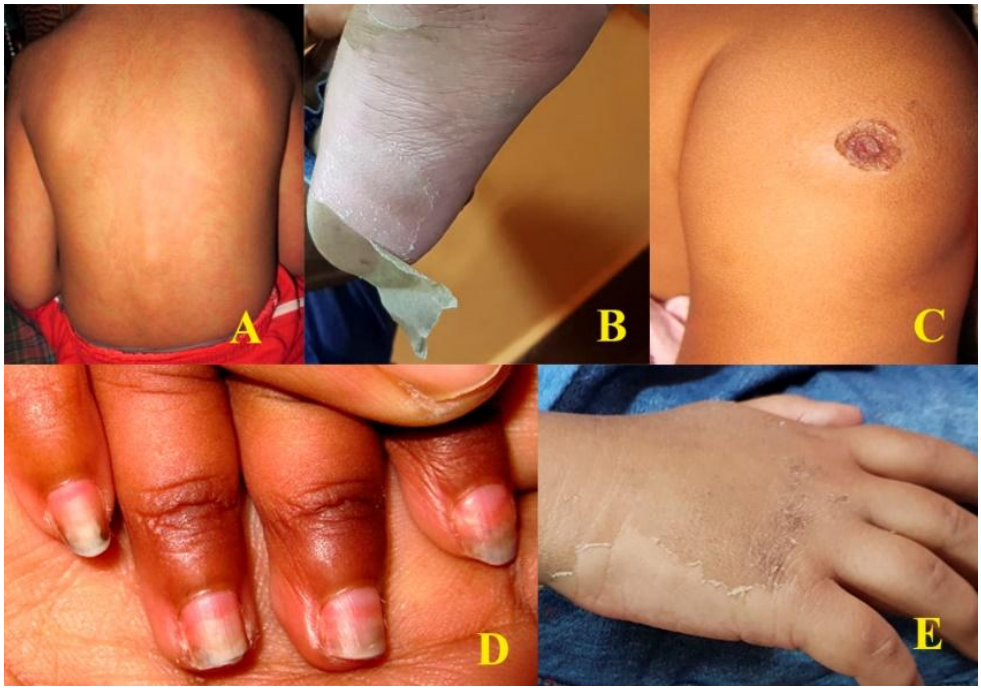

Fig.3 A-E; A: Erythematous maculo-papular rashes predominantly present on the trunk B: Exfoliation starts as periungual and then to entire sole and palm in severe cases C. Erythema around the BCG scar turning to mild ulcerative changes. D: Chromonychia-Striking brownish orange colour change of nails in acute phase. E: Exfoliation may extend to dorsum of hand in later phase

6.3 Myocardial involvement in Kawasaki Disease

Myocarditis is a well-recognized component of Kawasaki disease, with left ventricular dysfunction occurring in more than half of the patients during the acute phase of the disease, and may be transient. In KD, myocarditis develops even earlier than epicardial coronary arteritis; it peaks by disease day 10 and then disappears gradually after day 20. Inflammatory cell infiltration, consisting mainly of lobulated leucocytes and large mononuclear cells, was seen in the myocardial interstitium in all cases. (27, 28) Cardiac MRI is considered the Gold standard noninvasive test for diagnosing of Myocarditis. Augmented inflammatory condition can be revealed by increased intensity of T2 W images.Severity of detecting edema in

myocardium in acute phase of Myocarditis is 84% with specificity of 75%. Multiple foci of Hyper-enhancement in the myocardium during early Gadolinium enhancement EGE, consistent with Myocarditis. Though MRI gives diagnostic confirmation, echo scan is sufficient to rule out myocarditis.Cardiovascular biomarkers for myocarditis in KD are CKMB, Cardiac troponin I (25-35% elevated in biopsy proved myocarditis). N-terminal pro-B-type Natriuretic peptide (NT-pro BNP) and soluble ST2 (sST2) were elevated in acute vs. convalescent KD. (31) When the titre of Pro BNP is over 450 pg/ml and the patient probably has an abnormal ECG, is most likely to have myocarditis. Echocardiographic features of myocarditis are pericardial effusion, left ventricular systolic dysfunction evidenced as low ejection fraction, mitral regurgitation. The overall sensitivity of echo in picking up CAL is 95%. Sensitivity will decrease when lesions ate the distal area, then we advise for MD CT.

6.4 Rare associations with Kawasaki disease (32-35)

- Kawasaki patient rarely present with hypotension so called Kawasaki shock syndrome. And hyponatremia is a presenting symptom. Hence checking for electrolyte during acute phase is justifiable.
- Rarely papillary edema can develop. Hence Fundus exam also necessary to r/o papilledema.
- Bullae lesions, Gangrene, jaundice, interstitial nephritis, cystic fibrosis, varicella infection, auto immune haemolytic anemia etc.
- Kawasaki Disease may present as Acute Intestinal Obstruction.
- Kawasaki Disease complicated with Macrophage Activation Syndrome; Macrophage activation syndrome (MAS), also known as secondary hemophagocytic lympho-histiocytosis, is a rare and potentially fatal complication of Kawasaki disease (KD). The persistence of fever with splenomegaly, hyperferritinemia, thrombocytopenia,

and elevated aspartate aminotransferase (AST) should prompt the consideration of MAS complicating KD.

- Kawasaki disease may associate with hepatobiliary involvement.
- Adult-onset Kawasaki disease (mucocutaneous lymph node syndrome) and concurrent Coxsackievirus A4 infection.
- Kawasaki disease followed by Behcet's disease. Behcet's disease is a rare systemic vasculitis of unknown origin HLA-B51 allele located on chromosome 6p has been the most strongly associated risk factor for Behcet's disease. 5- Year old boy manifested signs and symptoms of KD with history of Bechcet's disease at 6months prior to KD. HLA-B51 may associate rarely with KD. (unpublished clinical data reported from a Canadian patient to KD foundation)
- Kawasaki disease may present with haemorrhagic pleural effusion.
- Meningococcal group A sepsis associated with rare manifestations and complicated by Kawasaki-like disease.
- Laboratory investigations to be done from the day of suspicion of KD till discharge is essential for the appropriate treatment, follow up and evaluation forthe treatment response. (Table 7)

TABLE 7. LABORATORY INVESTIGATIONS
Haemoglobin, Complete blood count
Platelet count to be repeated every 2-3 days to see the rising trend (Thrombocytosis)
ESR, CRP, ASO
Sodium, Potassium, Pro BNP
Liver function test; Bilirubin, Albumin, SGPT, SGOT,
NS1 antigen and dengue IgM, IgG serology,

if fever persist for > 5-days with profound Thrombocytopenia detects
Serum Ferritin
Urine routine
Non invasive tests; Ultra sound abdomen, ECG
First Echocardiogram at 5-7days of acute stage or as soon as you diagnose KD as a baseline echo, **if first echo is normal repeat after 5 days**

6.5 Serum biomarkers for Kawasaki disease

Current evidence suggests that NT-pro-BNP may be used as a diagnostic tool for KD. NT-pro BNP has high diagnostic value for identifying KD in patients with protracted undifferentiated febrile illness. (NT-pro BNP 1 Year >550PG/ML, 1-2Y >202PG.ML; 2-3 Y>189Pg/ml; >3y 152PG/ML). Positive results with ECG changes suggested that early evidence of KD myocarditis (36-38). Other importantlaboratory investigations routinely to be performed in all cases of suspected and diagnosed cases of KD are given in **Table 7.**

6.6 CORONARY ANEURYSMS

The 2017 AHA guidelines emphasized the application of Z scores for coronary artery evaluation and classified the severity of coronary abnormalities by using Z scores. Coronary Z scores of +2.5, +5.0, and +10.0 were recommended as the cut-off points for small, medium-sized, and giant coronary aneurysms, respectively **(Table 8).** These Z scoring systems are usually applied for the RCA, LMCA, and LAD (PSAX VIEW). Other coronary segments such as circumflex can be evaluated by comparing them to adjacent segments. (39).

Table 8: Coronary z-score classification and timing of echocardiography

Coronary artery involvement	Z score/ diameter	Timing of coronary 2-D Echocardiography
No involvement	<2	1-week interval till discharge, 1month & 6month, 2-years to see intimal dysfunction
Dilatation	>2 to <2.5	1-2 week interval , 1month after treatment, 6month, then till resolving to normal
Small aneurysm	>2.5 to<5	2-week interval till no progression 1month, 6th month and then till resolving to normal, after 2 years of stopping ASA
Medium	>5 to <10/<8mm	2-week interval till no progression 1month, 6th month and then till resolving to normal, after 2 years of stopping ASA
Large/Giant	>10z/ >8mm	weekly till one month and then monthly till 3rd month, see for thrombus then every 6months plus ECG/ TMT for older children if needed/ MDCT

Giant Aneurysm

Giant aneurysm can occur in 1% of CAL and is defined as diameter >8mm or ≥ +10 z score by coronary artery measurement **(Figure 4)**. As per the echocardiographic follow up giant aneurysm will never resolve. In such cases long term antiplatelet and anticoagulant therapy is

needed, by keeping INR 2.2. Further follow up is very essential and must be monitored every 4-6 months with ECG, Echo and TMT (39).Severe long-term complications can occur such as coronary artery stenosis resulting ischemic heart disease.Smooth muscle cells can migrate into intima producing myo-intimal proliferation; large amount of extracellular matrix and fibrosis results in calcification. Long term follow-up Studies done by Kato et.al showed calcification 12% at 5y, 44% at 10 y, 94% at 20 y after diagnosis of KD.

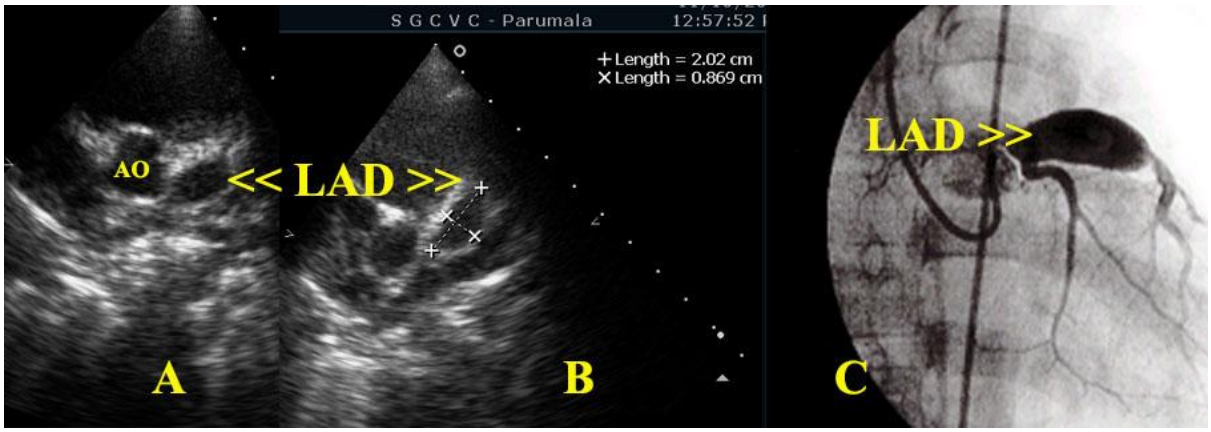

Figure 4 A-C: Giant coronary artery aneurysm (Z score >10). A-B; standard short axis view modified at the aortic valve level (AO) in 2-D Echocardiogram; Proximal segment of left anterior descending artery (LAD) with giant aneurysm marked (<<LAD>>) measuring 20x8.6mm. C; Coronary artery angiogram same case showed fusiform giant aneurysm of the proximal segment of LAD with normal left main and circumflex artery.

Non-Giant coronary aneurysm

Most CAA from KD is small to medium sized. Regression can occur 50-60% within 1-2 years.Factors associated with regression are less than1 year of age.Fusiform aneurysm gets resolved faster than saccular one. Smaller ones and distal CA Involvement will have faster regression. Regression of aneurysm is usually by intimal proliferation.

Accelerated Atherosclerosis

Persistent abnormal vascular wall morphology and dysfunction due to SMC proliferation and fibrosis of coronary walls may predispose early atherosclerosis. A 10-year FU study IVUShowed various degrees of intimal thickening at the site of regression. Endothelial dysfunction was proved in the form of increased constriction with acetylcholine and poor dilatation with isosorbide dinitrate. Transient dilatation didn't show any long term ischemic findings. In children atherosclerosis may occur after 10-12 years only. Fat restricted diet should be advised in later adolescent and middle-aged life.

7. Management of Kawasaki disease (28-29)

Goal of initial therapies in the acute phase is preventing coronary artery abnormalities by reduction of inflammatory response to the endothelium. Hence we should prevent inflammatory response by administering initial well accepted gold standard regime such as intra venous immunoglobulin and aspirin. The single dose of IVIG (2 g/kg) administered over 10-12 hr plus aspirin.IVIG should be administered as early as possible within 10 days of fever onset. For children with a diagnosis of KD after 10 days of fever and symptoms of an ongoing inflammatory process such as high CRP, ESR etc. IVIG should nevertheless be administered as soon as possible, even up to 20 days is acceptable. IVIG is not required for patients with low inflammatory markers, normalization of laboratory tests, and normal echocardiographic results in cases of presentation after 10-12 days.IVIG exerts anti-inflammatory effects. Possible mechanisms of IVIG include the modulation of cytokine production, neutralization of toxins, pathogenic agents. Fc receptors, augmentation of regulatory T cell activity, and suppression of antibody synthesis. Even with IVIG infusion,approximately 20% of patients may develop transient coronary dilatation and will resolve within 3-6 months of time., 5% of patients develop coronary aneurysms, and 1% of patients develop giant aneurysms after 1 month of KD onset.

ASA has been used in treatment of KD for many years. Although ASA has important anti-inflammatory activity (at high doses) and antiplatelet activity (at low doses), it does not appear to lower the frequency of development of coronary abnormalities. In acute phase Aspirin 60 mg/kg /Body weight/dayin 6hrly is acceptable dose even though some countries using higher dosagestill child become afebrile for at least 48hrs., sometimes even up to 3 days depends on the severity of CAL. In order to avoid gastritis in children, Aspirin can be given along with sucralfate or with antacids or other proton pump inhibitors as per your choice.Then Aspirin dosage should be adjusted to a low dose such as 3 to 5 mg /kg/day as single dose, once after the fever subsides at least for 48 to 72 hours of IVIG infusion.If no Coronary artery lesions, Aspirin should continue till 6-8wks.KD patients with coronary artery abnormalities must be administered medications for thrombosis prevention. Low doseaspirin is sufficient for prophylaxis of thrombosis in KD patients with coronary artery dilation only or small coronary artery aneurysms (Z 2.5 - <5). For KD patientswith medium-sized coronary artery aneurysms (Z 5.0 - < 10 and diameter <8 mm), dual antiplatelet agents use may be consideredsuch as Clopidogrel (dosage 0.2 – 1mg/Kg/Body weight) or Dipyridamole tablet also acceptable (1mg/Kg Body weight). For KD patients with a giant aneurysm (Z score >10 or diameter 8 mm), administering one anticoagulant, such as low-molecular-weightheparin (LMWH) or warfarin is reasonable. The recommended therapeutic target in the United States is 0.5 - 1.0 of activated factor Xa level for LMWH or the internationalnormalized ratio (INR) of 2-2.2 for warfarin. (19, 28).

Recent review on pathogenesis again prompts us to investigate **new drugs in KD** effectively TNF-α is a pleiotropic inflammatory cytokine that has been strongly implicated in the development of aneurysm formation in patients with KD.**Infliximab and Etanercept** are

examples of these TNF-α receptor antagonists. Etanercept, although a TNF-α antagonist, has different mechanisms to infliximab. Infliximab is a chimeric monoclonal immunoglobulin -G (IgG) antibody that targets transmembrane TNF-α. This damages the cells which express TNF-α, including cardiomyocytes (40-42). On the other hand, etanercept is a soluble fusion protein receptor that works more broadly on TNF (both TNF-α and lymphotoxin), and binds to only circulating TNF-α, thereby avoiding the adverse effect seen in infliximab. But we need more studies and both drugs plays important role as a pharmacological agents in recrudescent fever after first dose of IVIG or as a first line therapy. Markedly activated neutrophils or high plasma neutrophil elastase in patient with KD have been implicated in poor response to IVIG. **Ulinastatin** is a urinary tripsin inhibitor and has a property to inhibit neutrophil elastase.Treated with Ulinastatin as Initial treatment for KD, resulted in lower incidence of CAL in which 3% as opposed to 7% in control group.**Methotrexate** is a folic acid antagonist suppresses lymphocyte proliferation and has role in modulating cytokines especially IL-6 highly expressed in KD. Inositol Triphoshate 3-Kinase C act as a negative regulator of T-cell activation and activated T cells may play a pivotal role in pathogenesis of KD. **Cyclosporin** will suppress the activity of T cell.

Studies have demonstrated the pivotal role of Tumour Necrosis Factor (TNF)-a-mediated matrix metalloproteinase (MMP)-9 activity, in modulating key pathogenic stages of disease leading to coronary artery damage and also in the pathogenesis of elastin breakdown in a murine model of KD, Lactobacilluscaseicell wall extract-induced coronary arteritis. **Doxycycline** inhibits T cell activation and TNF-a production in peripheral immune cell and also inhibits directly MMP-9 enzymatic activity derived from TNF-a-stimulated vascular smooth muscle cells. Therefore, doxycycline can mitigate TNF-a-induced MMP-9-mediated coronary elastin breakdown and improve coronary outcome. **Antioxidants** such as of vitamin

A,C& E has a greater role in mitigating coronary artery lesion as an add on drug therapy. (42) Additional IVIG shows 71% response & 30% resistance. In such cases **Steroid pulse therapy (Methyl Prednisolone**) to resistant IVIG cases may give 100% response. Treatment protocol with dosages of medications given in Table 9.

Table 9; Treatment protocol of KD in acute phase

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1. **IVIG 2g /kg BW as single dose over a period of 10- 12 hrs (it can be given from the day of diagnosis usually after 5days of fever and even up to 18days in cases of late diagnosis. But the evidences of high inflammatory markers mandatory.**
2. **Aspirin 60 mg/kg /Body weight/dayin 6hrly with sucralfate or with antacids /ranitidine or other proton pump inhibitors as per your choice till child become afebrile for at least 48-72hrs.**

- **Aspirin treatment should be adjusted to a low dosage 3 to 5 mg /kg/day as single dose, once the fever subsides atleast for 48 to 72 hrs of IVIG infusion.**
- **If no Coronary artery lesions, Aspirin should continue till 6-8wks**
- **If coronary artery is involved, continue Aspirin till CAL resolves including intimal irregularities and thickening observed by 2-D echocardiogram follow up.**
- **For the giant aneurysm, Aspirin should be continued as lifelong therapy.**
- **With Coronary artery lesion excluding simple ectasia, add clopidogrel 0.2 to 1mg/kg/day max 75mg/day till the resolution of CAL by 2-D Echo follow up**

3. **With Giant aneurysm; Add warfarin (keep INR 2.2)/Coumadin/low molecular weight Heparin. LWMH is reasonable to administer in cases with Z SCORE >10**

- ***Infliximab may also be considered as first line of therapy when cases admitted with diagnosis of severe CAL and in anticipated IVIG resistant group. Infliximab will be more economical in older children than IVIG.***

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7. Resistant KD

Additional IVIG shows 71% response & 30% resistance. In such cases Steroid pulse therapy (Methyl Prednisolone) to resistant IVIG cases may give 100% response. Authors feel that we should start combination of drug therapies in in all IVIG resistant cases, in which steroid pulse therapy could be essential to prevent or further damage of coronary arteries (28,46). We don't want to see further risk in developing coronary aneurysms in recrudescent fever. Management protocol for IVIG resistant group is given in **Table 10** as per the personal experiences and may vary from person to person. CRP level of >8mg/dl after initial IVIG are likely to fail additional IVIG. In older children plasma exchange may be considered as another mode of treatment if you have facility for plasmapheresis under an experienced hematologist to remove circulating immune complexes, thus we can save the cost of IVIG especially in developing countries like India. Younger children cannot undergo plasmapheresis due to various procedural reasons. Different scoring systems were developed by various authors as per their experiences. **Table No.11**

8. KD Shock syndrome

The incidence of KD shock syndrome (KDSS) is estimated to be ≈7%.118,119 KDSS can be defined as the presence of hypotension and shock requiring the initiation of volume expanders, the infusion of vasoactive agents, or transfer to intensive care units. Shock in KDSS is often moderate, with low lactate values and the need for treatment with inotropic

and vasopressor agents. Although hemodynamic instability generally improves quickly once therapy with diuretic agents and vasopressor agents is initiated, a mild degree of ventricular diastolic dysfunction can persist after acute management. The causes of KDSS may involve the release of endogenous molecules that mediate a decrease in peripheral vascular resistance, myocardial dysfunction from myocarditis with or without myocardial ischemia, and capillary leakage, but the exact underlying mechanisms remain unclear. KDSS is often associated with more severe laboratory markers of inflammation and higher risk of coronary arterial dilation. Such cases are also more likely to be resistant to IVIG therapy and to require additional anti-inflammatory treatment(28).

TABLE. 10 FIRST LINE THERAPY IN RESISTANT KAWASAKI DISEASE

(Modified from AHA)

Second dose of IVIG	**2 gram /Kg/body weight**
IVIG + Prednisolone	**IVIG: 2 g/kg IV + Prednisolone 2 mg/Kg/day, divided every 8-hourly until afebrile, then prednisone orally until CRP normalized, then taper over 2–3 week**
IVMP	**Advised not with IVIG but can be givenseparately Intra venous methyl prednisolone (IVMP) 30 mg/Kg/ body weight over 2-3 hours x 3days.**
Then followed by oral 2-4weeks	
or Infliximab*	**5 mg/Kg/body weight single infusion x 2hrs + IVMP**
or Etnarcept	**0.8 mg/kg/Bodyweight, Sub cutaneous/week +IVMP**
or Ulinastatin	**20000 -30000 unit/Kg/ body weight OD IV x 3days + IVMP**

Cyclosporin-a 3-8 mg/kg/ body weight /day PO x 5-6 days depends on a febrile period(keep serum level 400-500ng/ml).

Anakinra2-6 mg/Kg/day by subcutaneous injection

 # Plasma exchange and methotrexate/ may be the final choice for refractory KD.

*** Infliximab may be considered as preferred first line therapy in resistant KD (desired drug of Indian Society of Kawasaki disease). Steroid may beadded as per the severity of CAL.**

Table No. 11: Prediction scoring Systems for IVIG Resistant cases

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1.Kobayashi score (≥5 points; sensitivity 76%, specificity 80%)

Na	≤133 mmol/L	2
AST	≥100 IU/L	2
Day of starting treatment (or diagnosis)		
	Day 4 after onset or earlier	2
Neutrophils	≥80% 2	
CRP	≥10 mg/dL	1
Platelets	≤300,000/μL	1
Age (months)	≤12 months	1

2.Egami score (≥3 points; sensitivity 76%, specificity 80%)

ALT	≥80 IU/L	2
Day of starting treatment (or diagnosis) Day 4 after onset or earlier		1
CRP	≥8 mg/dL	1
Platelets	≤300,000/μL	1
Age (months)	≤6 months	1

3.Sano score (≥2 points; sensitivity 77%, specificity 86%)

AST	≥200 IU/L	1
Total bilirubin	≥0.9 mg/D	1
CRP	≥7 mg/dL	1

4.Sathoshi Sato Score (3 or >3)

Neutrophils	>75%	2
IL 6	>140pg/ml	2
Il-6	70-140pg/ml	1

9.Long-term Management of Kawasaki Disease: Implications for the Adult Patient

Many scoring systems are available to predict Unresponsiveness to IVIG Therapy threshold Point. Current long-term management protocols are calibrated to the degree of maximal and current coronary artery involvement reflecting the known likelihood of severe long-term cardiac complications. It has recently been suggested that all KD patients may be at potential risk of severe long-term cardiac complications. Based on the available evidence, patients with multiple large and/or giant CAA are at substantial risk of severe long-term

cardiac complications and should have regular specialized follow-up. Patients with transient or no CAA have not been reported to be at risk of severe long-term cardiac complications. The influence of KD on the atherosclerotic process remains sub-optimally defined, and should be the focus of future studies. It is generally accepted that patients with no or transient coronary artery dilation during acute KD, comprising 95% of individuals diagnosed with KD in the past 25 years, live with long-term cardiovascular health comparable to the general population. An intermediate group of patients, those with small to medium sized CAA that may or may not have regressed, have an unclear long-term prognosis and, hence, may receive suboptimal follow-up include TMT and ECG every 1-2 years.Crystal et al found coronary artery z-score regression in patients with normal acute-phase coronary arteries, suggesting that dilation is a common and spontaneously resolving characteristic of acute illness. As such, dilation is an acute-phase phenomenon of endothelial dysfunction and coronary artery deregulation, resulting in no permanent changes to the vasculature. However endothelial dysfunction may persist in some patients with aneurysmal coronary artery dilatation. (42, 43)

10.Long-term Fate and Complications of Giant CAA

Although rare, giant CAA (8 mm or z-score 10) are highly unlikely to resolve. They are associated with the most severe long-term complications, including progression to stenosis or occlusion, resulting in ischemic heart disease. Stenosis of persistent and regressed CAA may occur as a result of myo-intimal proliferation, an intrinsic process of post acute KD, in which smooth muscle cells migrate from the media to the intima, producing large amounts of extracellular matrix and fibrosis. This process may further result in calcification of the aneurysm site by a mechanism similar to arteriosclerosis, which may be accelerated with persistent inflammation in some patients. Calcification occurs primarily at the media-intimal or the subendothelial surface. Calcification is a prevalent and unique characteristic of giant

CAA; affecting 12% at 5 years, 44% at 10 years, and 94% at 20 years after diagnosis. (43,44) Thrombotic occlusions may also progress to calcification after the organization and recanalization of a non-occlusive mural thrombus. Myocardial infarction is the major cause of death from KD, resulting either from sudden thrombotic occlusion of a vessel, or gradual stenotic occlusion. (45). We should be careful in monitoring such high-risk cases with regular ECG, exercise test and echocardiogram. In acute MI or ischemia, infants or children will present as severe cry, vomiting abdominal pain even shock. Older children may complaints of chest pain. Symptoms in MI and findings in ECG are given in **Table 12.**

Routine investigations in such cases with Tropi I and CKMB are necessary. therapy with tissue-type plasminogen activator (tPA) is the most commonly administered therapeutic regimen for occlusive or near-occlusive coronary artery thrombosis in infants and children. A common regimen of tPA is 0.5 mg/kg/hr over 6 hours. An alternative regimen of tPA used in adult coronary artery thrombosis, is 0.2 mg/kg intravenously (maximum 15 mg) stat, then 0.75 mg/kg over 30 minutes (maximum 50 mg) followed by 0.5 mg/kg over 60 minutes (maximum 35 mg). It should be administered together with low-dose ASA and low-dose intravenous heparin (10 U/kg/hr) with careful monitoring of coagulation parameters to prevent bleeding, maintaining the fibrinogen level >100 mg/dL and platelet count >50 000/mm^3. After completion of tPA, heparin dosage is increased as appropriate for age. The coronary artery thrombus should be reassessed with echocardiographic imaging after completion of the tPA infusion. (28)

Table 12. Symptoms of Myocardial Infarction & ECG findings in childern

SYMPTOMS	ECG CHANGES
• VOMITING	• ST/T CHANGES; T INVERTION IN

• **CHEST PAIN** • **SEVERE CRY** • **SHOCK** • **ABDOMINAL PAIN** • **ARRHYTHMIA**	**II, III, AVF** • **Q IN II, III, AVF INDICATE INFRACTION** • **PEAKED J POINT ELEVATION INDICATE ISCHEMIA** • **ELEVATION/ DEPRESSION OF ST SEGMENT V1-V3** • **WIDE QRS >35MS, I AVL, V5, V6** • **PROLONGED QTC >480 ,** • **VENTRICULAR TACHYCARDIA**

Optimal definition of CAA to be small if the z-score is > 2.5 to <5.0, large if the z-score is >or5.0 to <10.0, and giant if the z-score is > or10.0. This classification seems to appropriately apply to the circumflex branch despite a lack of normal values for this branch. The current AHA classification might not accurately classify CAAs in KD patients. Accurate classification is important for defining management and prognosis consistently across patient age and size. Based on studies reviewed in this meta-analysis, and the significant benefit in terms of reduced myocardial infarction and death, long-term oral anti-coagulation with warfarin together with aspirin appears to be the current best management of children with giant coronary arteries. (44- 46). All patients should be counseled in preventive care with regards to hyperlipidemia, hypertension, diabetes, obesity and physical activities.

11. Vaccinations during therapy

For patients who have received high-dose IVIG, immunization with measles, mumps, rubella, and varicella vaccines should be delayed for 11 months after IVIG infusion.Reye syndrome is

a risk in children who receive salicylateswhile they are experiencing active infection withvaricella or influenza and has also been reported in patientstaking high-dose ASA for a prolonged period oftime after KD. The low-dose therapy used for antiplateleteffect has not been associated with the developmentof Reye syndrome. In the patient who presentswith influenza and KD, administration of high-dose IVIGwithout aspirin and use of alternative antipyretic drugs(ie, acetaminophen) as needed for fever should be considered.An alternative antiplatelet agent should be consideredfor a minimum of 2 weeks. All children ≥6 months should receive a seasonal influenzavaccine, as should their family members. Onlyinactivated vaccine should be administered to childrenon aspirin therapy.(28)

12. COVID-19 AND KAWASAKI DISEASE

Confirmatory rapid PCR test was positive for SARS-CoV-2 in few children of KD cases during Covid-19 epidemic.(47)This RNA virus association had been observed with KD few years ago. (48-51) Circulating immune complexes (ICs), triggered by infectious agents, bacteria, or viral or other unknown causes, have been detected in the early phase of KD already known to us, implicating that immune-pathologic mechanisms might be involved in the pathogenesis of vasculitis in KD. (5-12) SARS-CoV-2 mimicking symptoms and signs of KD where immune-pathological mechanism could be same. Still this is not a particular causative agent to stress over etiopathogenesis on KD, but may consider as a one among the many trigerring agents for circulating immune complex producing vasculitis. As far as my understanding no authors published (THIS LINE MAY CHANGE AT THE TIME OF PUBLISHING) any coronary artery lesions in cases with positive SARS-CoV-2 which is more important to prove coronary artery affinity like in KD. We do not know why particular immune complexes disease attacking mainly coronary endothelium, could be readily triggers

a host immune response in genetically susceptible children and genes implicated in susceptibility to KD with replication. Family linkage studies and genome-wide association studies with subsequent validation studies have implicated single-nucleotide polymorphisms in six genes or gene regions**. (5,10)** These polymorphisms likely vary across populations and results suggest that KD susceptibility and disease outcome, including aneurysm formation and response to IVIG, are influenced by variants in several different genes and signalling pathways. (28)

Many authors also noted that Covid-19 can produce myocarditis in children. (52, 53) At the same time all cases with myocarditis didn't manifest signs and symptoms to fullfill the criteria for KD. Myocarditis in children can occur with many viral or bacterial diseases, and also will manifest in KD prior to epicardial coronary arteritis appear. Published data indicate that myocardial inflammation can be documented in 50% to 70% of patients using gallium citrate Ga 67 scans and technetium Tc 99m–labelled white blood cell scans. (28) Acute LV dysfunction is generally transient and responds readily to anti-inflammatory treatment. The rapid improvement in LV function differs from that observed in other causes of myocarditis. Myocarditis in KD likely improves rapidly as the inflammatory process subsides because it results from interstitial edema and inflammation and only rarely from myocardial cell necrosis. (28) Hence LV function study by routine Simpson method or Global longitudinal strain (GLS) by 2-D echocardiography in KD, and also in all other suspected viral illness including Covid-19 positive cases is essential. In such occasion I personally suggest that pediatricians should seek the help of a cardiologist to evaluate LV function by at least two or three follow up.

In one study D-Dimer was investigated and which was within normal limit. (D-dimer 3285-7180). In adult cases many clotting issues reported and thrombosis occur in most of the organs including heart results in stroke and myocardial infarction. Thrombotic episodes not published so far in children with Covid-19. All such cases with positive SARS-CoV-2 were well responded to IVIG and Aspirin. So that children with Covid positive, even without Signs and symptoms of KD, you may give a trial of same treatment protocol for KD to prevent or mitigate myocarditis and thrombotic episodes. IVIG will be certainly helpful in myocarditis in at least few cases as per our experiences. Role of HCQ in children yet to be proved. Possible mechanisms of IVIG include the modulation of cytokine production, neutralization of toxins, pathogenic agents. Fc receptors, augmentation of regulatory T cell activity, and suppression of antibody synthesis will certainly help in cases with SARS-CoV-2, and even in the situation of myocarditis.

Finally I conclude that we may add SARS-CoV-2 as one of the differential diagnosis of KD. Once the criteria is fulfilled for KD in Covid-19 cases, treatment protocol will be same as for KD. Veena. G. jones et.al, in their study, the patient was treated as per treatment guidelines, with intravenous immunoglobulin (IVIG) and high-dose aspirin (ASA), and subsequently reduced or resolved clinical symptoms in a case of KD with positive SARS-CoV-2. (51)

13. Conclusions

Kawasaki disease is a systemic vasculitis of unknown origin and circulating immune complexes triggered by infectious or non-infectious agents have been detected in the early phase of KD, implicating that immune-pathologic mechanisms might be involved in the pathogenesis of vasculitis in KD. The timely diagnosis of KD may be difficult in patients aged less than 6 months because of atypical presentations. KD should always be considered

in children with prolonged unexplained fever, thrombocytosis and peeling and with AHA special criteria. The role of the coronary Z scores has become increasingly crucial for managing and following up of CAL.Gold standard therapy for acute phase of KD is IVIG and aspirin, but add on therapy will certainly mitigate the severity of coronary artery vasculitis. IVIG plus low-dose prednisolone are both reasonable choices of treatments for patients with refractory KD.But KD society recommends infliximab as the first line and more economical in older kids in case of resistant KD. Giant aneurysm seldom resolves and needs lifelong antiplatelet and anticoagulant therapy. SARS-CoV-2 also may be considered as one of the differential diagnosis of KD.Timely diagnosis and an effective risk-stratified treatment regimen can reduce the incidence of coronary artery abnormalities. Long term follow up and parenteral counselling is most essential and crucial in KD coronary artery disease.

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