Kawasaki disease for dermatologists

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ABSTRACT

Kawasaki disease (KD) is a systemic vasculitis that mostly affects children below the age of 5. The vasculitis involves arteries of medium size, especially the coronaries. Various etiologies have been proposed including association with micro-organisms, bacterial superantigens, and genetic factors, however, the exact cause remains unknown. There is no specific laboratory test for KD. Diagnosis is clinical and depends upon the presence of fever for ≥5 days and 4 or more of five principal features, viz. polymorphous exanthem, extremity changes, mucosal changes involving the lips and oral cavity, bilateral bulbar conjunctival injection, and unilateral cervical lymphadenopathy. The term "incomplete KD" refers to the presence of fever and less than four principal clinical features. Recognition of this group of patients is important because it is usually seen in infants and risk of coronary abnormalities is increased probably because of delays in diagnosis. However, what appears to be "incomplete" at a given point of time may not actually be so because some of the features may have already subsided and others may evolve over time. Hence, a detailed dermatological examination is warranted in all cases, especially in incomplete KD, to ensure timely diagnosis. Although KD is a self-limiting disease in most patients, coronary artery abnormalities (CAAs) including coronary dilatations and aneurysms may develop in up to 25% of untreated patients. CAAs are the most common cause of morbidity and mortality in patients with KD. Treatment is aimed at reducing inflammation and consists of intravenous immunoglobulin (IVIG) along with aspirin. Despite treatment, some patients may still develop CAAs, and hence, long-term follow up is of utmost importance.

Key words: Coronary artery abnormalities, dermatologic manifestations, intravenous immunoglobulin, Kawasaki disease

INTRODUCTION

Kawasaki disease (KD) is an acute febrile multisystem vasculitis affecting most often children younger than 5 years of age.[1-4] It is characterized by fever, polymorphous exanthem, extremity changes, changes in lips and oral cavity, bilateral bulbar conjunctival injection, and unilateral cervical lymphadenopathy. In children with acute febrile illnesses where fever persists beyond 5 days, KD must be considered as a possible diagnosis.[5] Timely and appropriate treatment can decrease the risk of coronary artery abnormalities (CAAs), which otherwise may be seen in 15–25% of patients.[2,6]

Tomisaku Kawasaki [Figure 1], a young pediatrician, first reported KD in 1967. He presented 7 cases under the title "Non scarlatiniform syndrome with Desquamation from the fingertips" and later described his observations on 50 cases as "mucocutaneous lymph node syndrome."[7,8] Soon thereafter, children with a similar clinical profile were reported by Marian Melish [Figure 2] from United States.[9,10]

Though the first few cases of KD were reported from Japan followed by United States, it has since been described from all parts of the world, including developing countries.[5] Several centres in India have now been regularly reporting KD since the mid-1990s.[11-14] There has been a progressive increase in annual occurrence rate of KD in several developed countries, especially Japan.[15,16] Since the disease was first described in 1967, significant advances have been made

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Figure 1: Dr. Tomisaku Kawasaki

Figure 2: Dr. Marian Melish

in the understanding of its clinical, pathological, and epidemiological characteristics.

Epidemiology

KD is the most common vasculitic disorder affecting children across different races worldwide, although the risk is highest among Asians. Highest incidence of KD has been reported from Japan at 265/100,000 children below 5 years of age, followed by Korea and Taiwan.[6] Of all the children born in Japan, it is estimated that 1% would get KD by 10 years of age.[15] In Japan, Korea, and Taiwan, incidence of KD is above 50/100,000 children below 5 and has been progressively increasing. The incidence of KD in Japan has increased more than twice over the last 20 years.[15,16] In contrast, United States and Europe report an incidence of less than 30/100,000 children below 5 and the incidence seems to have plateaued over time.[16-18]

Age group

KD predominantly affects children aged less than 5 years.[3] However, it can affect older children and, sometimes, even adults. The peak age of onset of KD varies among different countries – United States reports peak age at 18–24 months, which is slightly higher as compared to Japan where it is 6–11 months.[2,4,19] At our centre, almost 30% of patients were above 5 years of age at diagnosis of KD.[20,21] The male:female ratio is 1.5:1.0.[5]

Seasonal variation

Seasonal variation has been noted in patients with KD in some countries. In Japan, majority of cases are clustered in January, June, and July, whereas in the United States, winter and early spring months account for the maximum number of patients with KD.[18,22] At Chandigarh, clustering has been observed during the months of October and May.[23] This seasonal variation in occurrence of KD has been linked to changes in tropospheric wind patterns but that does not explain seasonality of KD in every country.[24,25]

Etiopathogenesis

The exact etiology of Kawasaki disease is not known.[2,4,7] Various theories have been proposed including the role of micro-organisms and superantigens. An infective etiology can explain the clinical presentation with fever, exanthem, bilateral conjunctival injection, and cervical lymphadenopathy along with a self-limiting illness.[2,7] However, no definite organism has yet been identified.[26] Although an association with various organisms such as *Streptococcus*,[27] *Staphylococcus*,[27] Epstein Barr virus,[28] Coronavirus,[29] and Parvovirus[30] has been reported in some studies, a cause and effect relationship has not been established.

Bacterial superantigens (staphylococcal and streptococcal) have also been implicated in the pathogenesis of KD vasculitis because of the presence of excess of Vβ2 and Vβ8 T-cell receptor families in coronaries, intestinal mucosa, and blood.[31,32] This, along with occasional presentation similar to superantigen mediated toxic shock syndrome, favors the role of superantigens in the pathogenesis of KD;[33] however, these theories also remain unsubstantiated.

Several other novel hypotheses have also been proposed. Burns *et al*. have described how transportation of a probable

etiological agent (suspected fungal spore) through tropospheric winds has been linked to the occurrence of KD.[25] This fungal agent (perhaps a toxin) is believed to trigger an abnormal immune response in genetically susceptible hosts, which results in clinical manifestations of KD. Other than fungi, several different microbial agents may also trigger an immunologic response which manifests as KD.[3]

Pathology

The clinical manifestations in KD occur due to necrotizing systemic vasculitis affecting medium and small sized arteries, predominantly involving the coronaries.[34] Inflammatory infiltrate consisting primarily of IgA secreting plasma cells[35,36] and macrophages initially affects the microvasculature (arterioles, capillaries, and venules) and subsequently involves larger vessels. This inflammation, which is a panarteritis, may result in the weakness of vessel wall. The increased vascular fragility results in dilatation of the affected vessel wall, which in severe cases, results in formation of aneurysms. Thrombosis and aneurysms of the coronaries were first demonstrated at autopsy in patients with KD by Tanaka *et al*. from Japan.[37,38] Subsequent healing of the inflamed vessel may result in stenosis as well as thrombosis at the affected site, resulting in myocardial infarction at a later age.

Histopathological findings of skin lesions in KD show edema, dilatation of small vessels in papillary dermis, and infiltration of CD4+T cells and CD13+ macrophages in dermis and epidermis.[39] In addition, skin lesions have been shown to have interleukin-1α and tumor necrosis factor alpha (TNF-α) suggesting a role in the pathogenesis of KD.[39]

Genetics

Published literature on KD from Japan best documents the rates of recurrence and familial occurrence of KD; these rates may be lower among other populations. The recurrence rate of KD among Japanese is ~3%, and ~1% of cases have a positive family history.[3,40] KD occurs at a rate of 2.1% among the siblings of KD patients who had the disease within last 1 year. Increased rate of occurrence of KD in the siblings suggests an underlying genetic susceptibility, which interacts with etiologic agents in the environment.[23]

Certain HLA genes have been proposed to be linked with KD and increased risk of abnormalities affecting the coronary arteries; however, no definite contribution of HLA genes has been proved. Three important pathways have been reported to be involved in the pathogenesis of KD. These include single nucleotide polymorphism (SNP) in transforming growth factor β2 (*TGFβ2*) and *TGFβR2*, SNP in the gene encoding 1,4,5-inositol triphosphate 3-kinase C (*ITPKC*);[26] and SNP in the Fc gamma receptor IIa (*FCGR2A*) gene.[41] Further genetic studies may hold the key to our understanding of the pathogenesis of KD.

Clinical manifestations

The course of KD can be divided clinically into the following three phases [Figure 3].[4]

Acute febrile phase

It lasts for initial 10–14 days and is characterized by fever, redness of the eyes, inflammation of tongue (strawberry tongue) and pharyngeal mucosa, unilateral cervical lymphadenopathy, dry cracked lips, edema over the extremities, extreme irritability, and perineal desquamation. Myocarditis may occur commonly during the acute phase manifesting as tachycardia and congestive cardiac failure. Several other clinical features that may be seen during this stage include hydrops of gall bladder, sterile pyuria, and BCG site reactivation. However, these features do not figure among the criteria for diagnosis of KD.

Subacute phase

This phase lasts from week 2 to 4 after onset of symptoms. It is characterized by periungual desquamation and resolution of clinical findings seen during the acute stage. CAAs on echocardiography are most commonly seen during this phase. A small proportion of children may also develop arthritis involving one or more joints.

Convalescent phase

It is characterized by disappearance of all clinical signs and most children become asymptomatic. Acute phase reactants

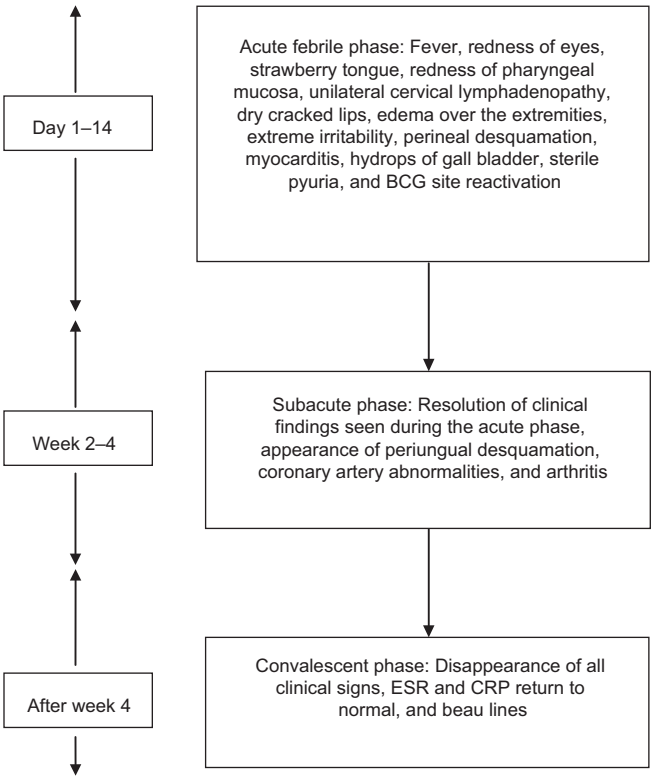

Figure 3: Flow chart showing the temporal course of Kawasaki disease

including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and platelet count usually return to normal. Beau lines (horizontal ridging of the nails) may appear during this phase.

Diagnostic criteria for Kawasaki disease

Diagnosis of KD depends upon:[3,4,42,43]

(A) Presence of fever for ≥5 days, and

(B) Presence of ≥4 of the following 5 principal clinical features:

1. Extremity changes
   Changes in acute phase: Erythema involving palms and soles;
   Edema over dorsum of hands and feet
   Changes in subacute phase: Periungual peeling of fingers and toes
2. Polymorphous exanthem
3. Non exudative injection of bilateral bulbar conjunctiva
4. Changes involving mucosa (lips and oral cavity): Erythema, dryness and vertical cracking of the lips, red (strawberry) tongue, injection of pharyngeal and oral mucosa
5. Enlarged cervical lymph nodes, usually unilateral (>1.5cm diameter)

(C) Other diseases with findings similar to those mentioned above should be excluded

In patients with fever and <4 principal clinical features, diagnosis of KD can be made if CAAs are observed on echocardiography.[43] Because there is no gold standard for diagnosis of KD, the sensitivity and specificity of diagnostic criteria is virtually impossible to define. It should, however, be noted that strict application of the abovementioned clinical criteria for diagnosis of KD would have high specificity but low sensitivity. And this may result in several children with KD being denied of treatment that can be potentially beneficial.

Fever

High grade fever, usually >40°C, and not responding to antipyretics and antimicrobials, is often the first clinical manifestation. Fever in patients with KD reflects underlying inflammation of vessel wall. It is usually accompanied by extreme irritability, which is more prominent in younger patients as compared to older children.

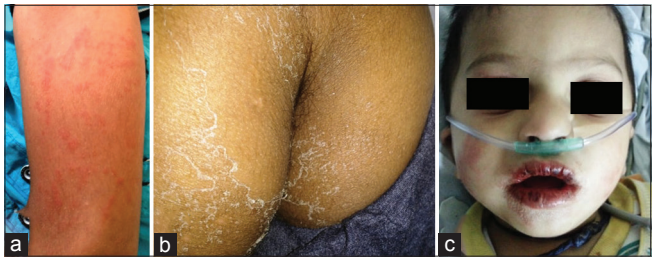

Figure 4: (a) Rash over extremities in a child with KD; (b) Perianal desquamation; (c) Dry, reddened, and vertically cracked lips

Rash

Rash in KD appears during the first few days of onset of fever (acute febrile phase). It is polymorphous, varying from macular to maculopapular or morbilliform, however, it is never vesicular. It most commonly begins on the trunk and spreads over the next few days to involve the extremities [Figure 4a]. Rash over the perineal area often undergoes desquamation during the first week of illness [Figure 4b]. It usually disappears with the resolution of fever.

Mucosal changes

Involvement of mucosa is characterized by vertically cracked lips which are dry and reddened [Figure 4c], strawberry tongue [Figure 5a], and erythema of oral and pharyngeal mucosa. These changes are seen during the acute febrile phase of KD. However, manifestations may fluctuate in the first 7–14 days of illness and do not occur in a particular order.

Conjunctival injection

Bilateral, nonexudative, bulbar conjunctival injection, and typically sparing the limbus (i.e., the area immediately surrounding the cornea) is common in KD [Figure 5b] during acute febrile phase. Conjunctival injection of KD must be differentiated from conjunctivitis (i.e., conjunctival inflammation with eye discharge) – the latter is never a feature of this condition.

Extremity changes

Erythema involving the palms and soles, and edema of the dorsum of hands and feet occur during the acute febrile phase of the disease. Subacute phase of KD is characterized by desquamation beginning at the tips of fingers and toes [Figure 5c]. Beau lines may appear during the convalescent phase as transverse ridges over nails [Figure 6a]. These develop as a result of arrested nail growth during the initial febrile phase of KD.

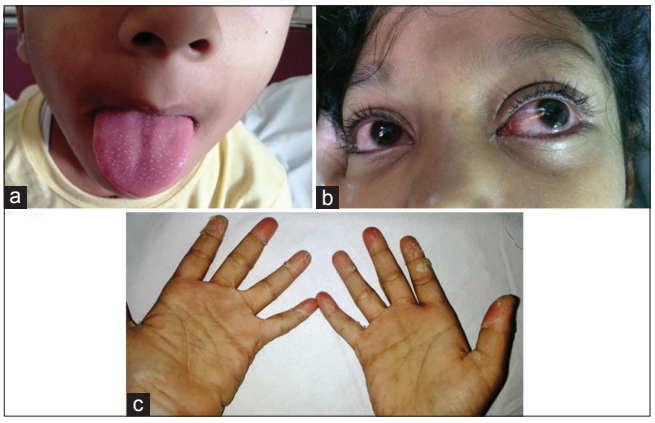

Figure 5: (a) Strawberry tongue; (b) Conjunctival injection; (c) Periungual desquamation

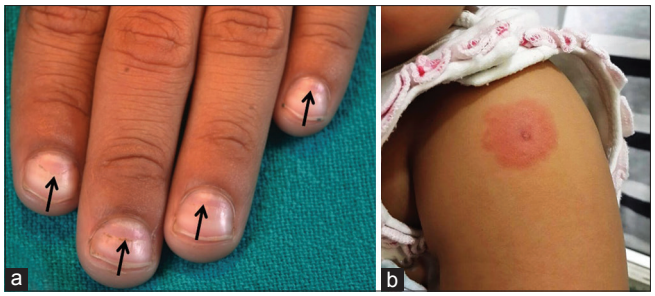

Figure 6: (a) Beau lines; (b) Induration at BCG inoculation site

Cervical lymphadenopathy

Lymphadenopathy in KD is characteristically unilateral and affects the cervical region during the acute phase of the disease. It is seen in 60–70% of patients with KD in Japan, and in less than 50% patients in United States.[1] Lymphadenopathy involving multiple lymph nodes and presence of splenomegaly are clinical features not usually seen in KD and, when present, should point toward an alternate diagnosis.

Other clinical manifestations of Kawasaki disease

Apart from principal mucocutaneous features, a subset of patients with KD may exhibit distinct dermatologic manifestations. Occurrence of psoriasiform eruptions during an episode of KD[44] and flaring up after KD[45] has been well-documented in literature. In addition, some reports suggest an increased incidence of atopic dermatitis among children with KD.[46] Rarely, erythema multiforme has also been described as a sign of KD.[47]

Patients with KD may have several additional findings involving other organ systems as well. These findings may create diagnostic difficulties for the treating physician and result in delays in diagnosis.

Other clinical findings in patients with KD include:[3,43]

1. Findings of the cardiovascular system
   Abnormalities of coronary arteries
   Aneurysms involving medium sized non-coronary arteries
   Congestive cardiac failure
   Myocarditis, pericarditis
   Peripheral gangrene
2. Findings of the musculoskeletal system
   Arthralgia
   Arthritis
3. Findings of the gastrointestinal tract
   Abdominal pain, vomiting, diarrhea
   Transaminitis, hyperbilirubinemia
   Hydrops of gallbladder
4. Central nervous system findings
   Aseptic meningitis
   Irritability that is often extreme
   Cranial nerve palsies
5. Genitourinary system
   Urethritis
   Sterile pyuria
6. Other clinical findings
   Erythema and/or induration at BCG inoculation site (Figure 6b)
   Anterior uveitis (usually mild)

Cardiovascular disease in Kawasaki disease

KD has surpassed rheumatic fever to become the leading cause of acquired pediatric heart disease in developed countries including North America, Europe, and Japan.[48] It may soon be the leading cause of acquired pediatric heart disease in developing countries as well.[49]

It is not often recognized that myocarditis is also an integral part of KD. It is usually asymptomatic but can clinically manifest in a small proportion of patients.[50] Asymptomatic myocarditis may be recognized by tachycardia (not explained by the degree of fever) and decreased systolic function of the left ventricle. KD may also present with pericarditis and pericardial effusion.[6] Recently, KD shock syndrome is being increasingly recognized in children who present with systolic hypotension.[51]

The most characteristic and clinically significant complication of KD is the occurrence of CAAs which can be seen in 15–25% of untreated patients.[2,6] The severity of CAAs may vary from asymptomatic coronary artery dilatation or aneurysms to giant aneurysms. Giant coronary aneurysms (>8 mm internal diameter) during the acute stage have a significant risk of thrombosis and rupture.[3,52] Kato *et al*. studied the outcome of coronary aneurysms in patients with KD in Japan.[52] Majority of coronary aneurysms show regression or a decrease in size over few months after an acute episode of KD. In patients with incomplete resolution of coronary aneurysms, stenosis may develop insidiously and present later in adulthood as coronary ischemia. Timely diagnosis and treatment of CAAs is therefore critical.[3,53]

Several other cardiovascular complications can also occur in children with KD. These include arrhythmias, abnormal QT dispersion, endothelial dysfunction, aortic stiffness, and sudden death.[3,54-56] This suggests that like many other vasculitides, KD is a more generalized disease process than usually recognized.

Incomplete Kawasaki disease

The term “incomplete KD” refers to the presence of fever and less than four principal clinical features of KD.[2,4] Recognition of such cases can sometimes be quite difficult.[57-59] It is important to remember, however, that not all clinical features of KD may be apparent at a given time. Some of the features may have already subsided and others may evolve over time. Hence, one should carefully observe and ask for signs and symptoms

suggestive of KD that may have already subsided. Incomplete KD is most commonly seen in infants,[60] and is often associated with development of CAAs.

Atypical Kawasaki disease

A child is said to have "atypical KD" when he/she presents with clinical manifestations suggestive of KD along with some unusual features. These atypical manifestations may include seizures, stroke, nephritis, and acute hepatitis.[2-4] Infants may present more commonly with atypical features and have increased predilection for CAAs.

Adult onset Kawasaki disease

Adult patients with KD have similar clinical features, including dermatologic manifestations, as in children. However, frequency of clinical signs may vary between the two populations.[61] Although rare, adult onset KD is associated with high frequency of cardiovascular involvement. Because of its rarity and need to exclude other differential diagnoses, adult onset KD is usually diagnosed late.

Recurrent Kawasaki disease

Nationwide epidemiological surveys of KD in Japan reveal a recurrence rate of approximately 3% with the highest incidence within 12 months of first episode. In addition, incidence is usually higher among children with cardiac sequelae during the first episode.[62] Clinical features, including dermatologic manifestations, during a recurrent episode of KD are similar to those seen in the first episode.

Differential diagnosis of Kawasaki disease

Differential diagnosis of KD include following infections, both viral and bacterial, immune system reactions, and rheumatic diseases which may cause signs and symptoms similar to KD:[4]

1. Infectious Conditions
   Viral: Adenovirus, measles, parvovirus, human herpes viruses (e.g., cytomegalovirus, herpes simplex virus)
   Rickettsial: Rocky Mountain spotted fever
   Spirochetal: Leptospira
   Bacterial: Streptococci, staphylococci
2. Reactions of the Immune System
   Diseases mediated by toxins (toxic shock syndrome)
   Stevens–Johnson syndrome
   Serum sickness
3. Rheumatic Diseases
   Systemic juvenile idiopathic arthritis
   Polyarteritis nodosa

KD may be difficult to diagnose and manage in resource limited settings[63] because of limited awareness, inability to gain access to appropriate investigations and treatment, and because of difficulty in distinguishing KD clinically from exanthemata, such as measles, which are endemic in many developing countries.[64]

KD must be included in the differential diagnosis of children where rash and fever persists beyond 5 days because fever generally settles within a few days in most exanthemata. From a dermatologist's point of view, it is important to distinguish KD from other infectious conditions, especially Stevens–Johnson Syndrome (SJS),[65] Scarlet fever,[66] and measles [Table 1]. Staphylococcal scalded skin syndrome (SSSS) may also be considered in the differential diagnoses in view of fever, irritability, and erythematous eruptions. However, lack of other mucocutaneous features, presence of a localized staphylococcal infection and skin tenderness, accentuation of rash in the flexures, and progression to superficial blister formation differentiate SSSS from KD.[67]

Table 1: Differentiating features between Kawasaki disease, Steven-Johnson syndrome, Scarlet fever, and Measles

	KD	SJS[65]	Scarlet fever[66]	Measles
Age group	Mostly below 5	All age groups	Mostly between 5-15 years	Most common in preschool children
Etiology/Causative organism	Unknown	Drugs (sulphonamides, anticonvulsants), Mycoplasma pneumonia	Streptococcus pyogenes	Measles virus
Nature of rash	Polymorphous, never vesicular	Atypical targets or purpuric macules, vesicles, tend to coalesce	Punctate erythema, "sunburn with goose pimples" or "sandpaper"	Macular, dull red papular, tend to coalesce
Distribution of rash	Begins on the trunk, spreads to extremities	Starts from the face and chest, spreads to whole body	First appears on upper trunk, generalizes within a few hours or over 3-4 days	Starts from the forehead and behind the ears, spreads downwards
Time of onset of rash	During first week of illness	7–10 days after drug exposure (range 5-28 days)	Within 24-48 hours after onset of symptoms	Develops on fourth day of fever
Other characteristics of rash	Non pruritic rash	Pruritis and cutaneous pain	Relative pallor around the mouth, desquamation after 7-10 days	Leaves fine desquamation of skin

INVESTIGATIONS

Laboratory examination

There is no specific diagnostic test for diagnosis of KD. However, there are certain laboratory markers which are seen during the different phases of the disease. The acute febrile phase is associated with laboratory parameters that suggest ongoing inflammation. These include an elevated ESR, raised CRP, leukocytosis with neutrophilic predominance, and thrombocytosis which, in severe cases, may reach levels as high as 100,0000/mm^3.[3] Some children may have normocytic, normochromic anemia. Presence of anemia and thrombocytopenia may suggest the development of macrophage activation syndrome, which can sometimes complicate the clinical course of KD.

Other laboratory abnormalities include sterile pyuria of urethral origin and elevated serum transaminase levels, with or without mild hyperbilirubinemia. Pyuria in a febrile child should alert the treating physician to the underlying possibility of KD – it need not always be due to urinary tract infection.[2,4]

Changes in serum lipid profile, including elevated triglycerides, and reduced high density lipoproteins may be seen during the subacute phase of KD.[3,68,69]. In some children, these can persist over extended periods of time.[70]

Imaging in Kawasaki disease

Two-dimensional transthoracic echocardiography has long been used for the assessment of CAAs in patients with KD. CAAs detected on echocardiography may include aneurysm and/or dilatation of left main coronary artery (LMCA), left anterior descending branch (LAD), and right coronary artery (RCA).[3] Abnormalities of the left circumflex artery (LCx) are more difficult to visualize. Coronaries are said to be dilated if their diameter is >1.5 times that of the adjacent vessel segment; or if the diameter is >3 mm in a child less than 5 years old; or >4 mm in a child ≥5 years of age.[3] Other corroborative findings on echocardiography include loss of normal tapering of the coronary arteries, increased brightness of the vessel wall, and pericardial effusion.

Coronary artery diameter should be assessed using z-scores. Children with KD need to be followed up with serial echocardiographs to monitor the CAAs. While echocardiography can visualize proximal segments of coronary arteries, it is not a good modality for distal segments of coronary arteries. Dual source CT coronary angiography (CTCA) is now being increasingly used as an imaging modality for the assessment of coronary arteries in KD.[71]

TREATMENT

The aim of treatment of KD in acute febrile phase is the reduction of inflammation in walls of the coronary arteries, thereby decreasing the risk of coronary thrombosis. In patients who develop aneurysms and/or dilatations of the coronary arteries, long-term therapy is directed at preventing myocardial ischemia.[3] Intravenous immunoglobulin (IVIG) is the mainstay of the treatment and is given at a dose of 2 g/kg, preferably within 10 days of the illness.[3,72-74] However, if patients present late during the course of the illness and there is evidence of ongoing inflammation, IVIG should not be withheld.[75] Response to IVIG is usually prompt; fever generally subsides before the end of infusion of IVIG and irritability decreases considerably. IVIG should be initiated slowly to prevent or minimize infusion reactions. Aseptic meningitis presenting as headache, vomiting, and irritability is another prominent adverse effect seen with IVIG. It can be prevented by slowing the rate of IVIG infusion and increasing the intake of oral fluids.

Acute phase treatment also consists of aspirin which is started in anti-inflammatory doses (30–50 mg/kg/day) and is continued for 48–72 hours after the child becomes afebrile. The dose of aspirin is then decreased to 3–5 mg/kg/day, which is maintained until the child has no evidence of CAAs by week 6–8 after the disease onset. It needs to be continued indefinitely in children who develop persistent CAAs.[3,5]

Most patients respond to IVIG and aspirin. However, in 10–15% of patients, fever may not subside or may recur.[2,3] Management of such patients can be difficult. Therapeutic options that are available include a repeat dose of IVIG,[76-78] administration of infliximab (TNF α blocker),[79,80] or methylprednisolone.[3] Algorithms for a classical case of KD and for incomplete KD are shown in Figures 7 and 8, respectively.

Disease course and prognosis

Mortality in KD has been reported at 0.014% in Japan.[3] At our centre, it is higher at 0.87%, probably due to delays in diagnosis, referral, and treatment.[81] The risk of development of CAAs can be brought down to less than 3% if the condition is diagnosed in time and treated appropriately.[3,82] After the initial echocardiographic evaluation of coronaries, regular assessment is done at 2 weeks and then at 6 weeks.[3] Frequency of further assessment depends on the status of the coronary arteries. Smaller aneurysms are more likely to resolve as compared to large aneurysms. Furthermore, age of onset of aneurysms less than 1 year, fusiform aneurysms, and aneurysms located in the distal coronaries have an increased likelihood of resolution.[3,4] Giant aneurysms are associated with the risk of thrombosis and stenosis, which may manifest clinically as arrhythmias, congestive cardiac failure, and myocardial ischemia.[53] Patients with coronary lesions should, therefore, be followed up with

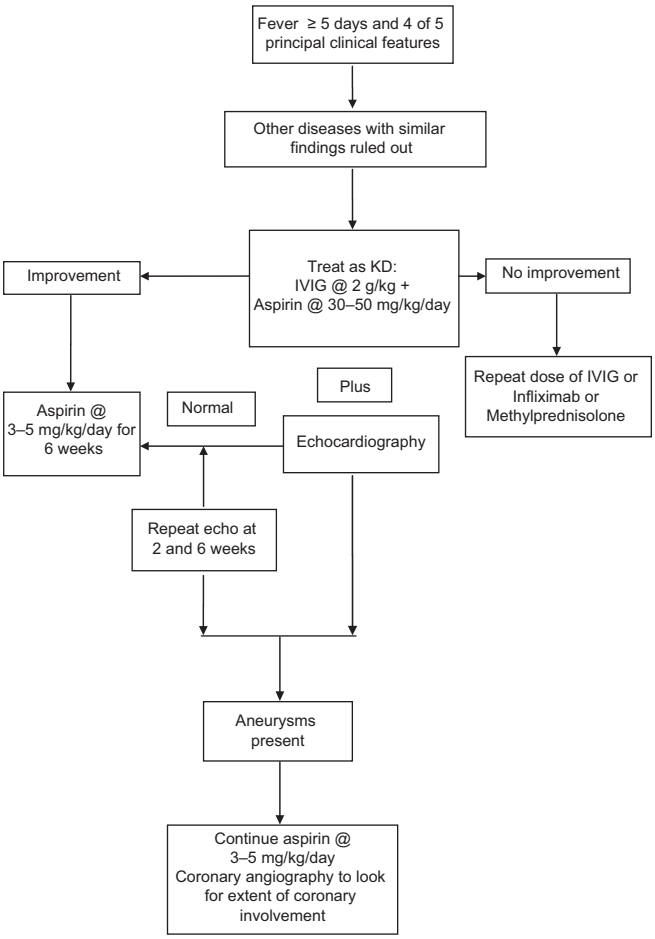

Figure 7: Algorithm for a classical case of Kawasaki disease

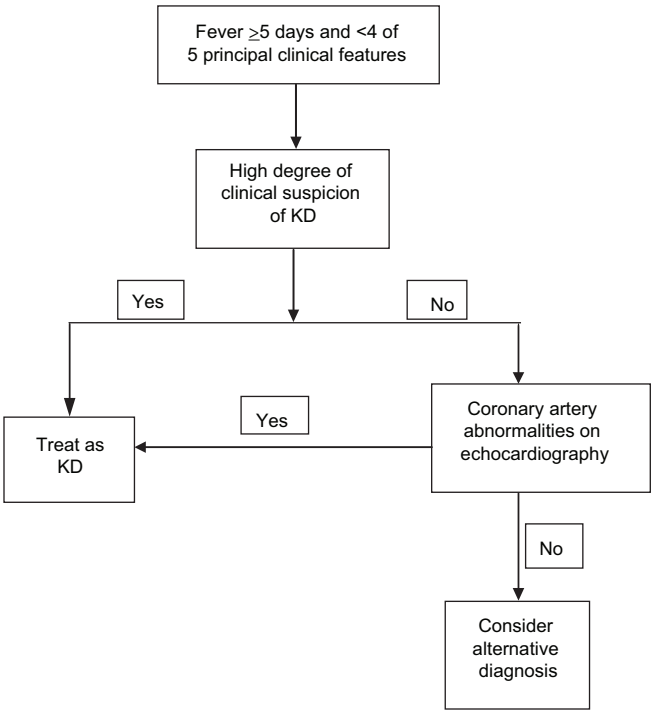

Figure 8: Algorithm for incomplete Kawasaki disease

regular echocardiography evaluation. It must be borne in mind that KD is a systemic vasculitis and not merely a disease that affects the coronary arteries. Recent literature suggests that KD can impact the cardiovascular system in several different ways and these sequelae may manifest several years later in young adulthood.[54-56,68-70] It is for this reason that long-term follow-up is mandatory for all children with KD, irrespective of whether or not they have CAAs.

Key messages for the dermatologist

1. KD is now the most common vasculitic disorder in children. Majority of patients are below the age of 5 years
2. It has been reported from all continents and is being increasingly recognized in several centres across India
3. KD should be considered in the differential diagnosis of all children who present with rash and fever that persists for 5 days or more. Rash in KD may be polymorphous but is almost never vesicular. In most exanthemata, fever generally settles within a few days
4. Other typical dermatologic manifestations include:
   a) Bilateral conjunctival injection
   b) Erythema, dryness, and vertical cracking of lips
   c) Strawberry tongue
   d) Injection of pharyngeal and oral mucosa
   e) Erythema over palms and soles
   f) Edema over the dorsum of hands and feet
   g) Periungual desquamation
   h) Beau lines
5. Children with rash and fever need to be jointly assessed by the dermatologist and pediatrician
6. Diagnosis of KD needs to be made promptly and appropriate treatment initiated early for preventing the dreaded coronary complications associated with the disease.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Kawasaki T. Kawasaki disease. Proc Jpn Acad Ser B Phys Biol Sci 2006;82:59-71.

2. Kawasaki T. General review and problems in Kawasaki disease. Jpn Heart J 1995;36:1-12.
3. Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, *et al*. Diagnosis, treatment, and long-term management of Kawasaki disease: A statement for health professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, American Heart Association. Pediatrics 2004;114:1708-33.
4. Son MB, Sundel RP. Kawasaki disease. In: Petty RE, Laxer RM, Lindsley CB, Wedderburn LR, Editors. Textbook of Pediatric Rheumatology. 7th ed. Philadelphia: Elsevier Saunders; 2015. p. 467-83.
5. Singh S, Kawasaki T. Kawasaki disease-An Indian perspective. Indian Pediatr 2009;46:563-71.
6. Singh S, Sharma D, Bhattad S, Phillip S. Recent Advances in Kawasaki Disease-Proceedings of the 3rd Kawasaki Disease Summit, Chandigarh, 2014. Indian J Pediatr 2016;83:47-52.
7. Kawasaki T. Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children. Arerugi 1967;16:178-222.
8. Kawasaki T, Kosaki F, Okawa S, Shigematsu I, Yanagawa H. A new infantile acute febrile mucocutaneous lymph node syndrome (MCLS) prevailing in Japan. Pediatrics 1974;54:271-6.
9. Burns JC, Kushner HI, Bastian JF, Shike H, Shimizu C, Matsubara T, *et al*. Kawasaki disease: A brief history. Pediatrics 2000;106:E27.
10. Melish ME, Hicks RM, Larson E. Mucocutaneous lymph node syndrome in the US. Pediatr Res 1974;8:427A.
11. Narayanan SN, Krishna V, Sabarinathan K. Kawasaki disease. Indian Pediatr 1997;34:139-43.
12. Paul DK, Gupta A, Lahiri M. Kawasaki disease in Calcutta. Indian Pediatr 2000;37:1264-5.
13. Singh S, Kumar L, Trehan A, Marwaha RK. Kawasaki disease at Chandigarh. Indian Pediatr 1997;34:822-5.
14. Singh S, Kawasaki T. Kawasaki Disease in India – Lessons Learnt Over the Last 20 Years. Indian Pediatr 2016;53:119-24.
15. Makino N, Nakamura Y, Yashiro M, Ae R, Tsuboi S, Aoyama Y, *et al*. Descriptive Epidemiology of Kawasaki Disease in Japan, 2011–2012: From the Results of the 22nd Nationwide Survey. J Epidemiol 2015;25:239-45.
16. Singh S, Vignesh P, Burgner D. The epidemiology of Kawasaki disease: A global update. Arch Dis Child 2015;100:1084-8.
17. Holman RC, Belay ED, Christensen KY, Folkema AM, Steiner CA, Schonberger LB. Hospitalizations for Kawasaki syndrome among children in the United States, 1997-2007. Pediatr Infect Dis J 2010;29:483-8.
18. Chang RK. The incidence of Kawasaki disease in the United States did not increase between 1988 and 1997. Pediatrics 2003;111:1124-5.
19. Yanagawa H, Yashiro M, Nakamura Y, Kawasaki T, Kato H. Results of 12 nationwide epidemiological incidence surveys of Kawasaki disease in Japan. Arch Pediatr Adolesc Med 1995;149:779-83.
20. Singh S, Bansal A, Gupta A, Kumar RM, Mittal BR. Kawasaki disease: A decade of experience from North India. Int Heart J 2005;46:679-89.
21. Singh S, Gupta MK, Bansal A, Kumar RM, Mittal BR. A comparison of the clinical profile of Kawasaki disease in children from Northern India above and below 5 years of age. Clin Exp Rheumatol 2007;25:654-7.
22. Holman RC, Curns AT, Belay ED, Steiner CA, Schonberger LB. Kawasaki syndrome hospitalizations in the United States, 1997 and 2000. Pediatrics 2003;112:495-501.
23. Singh S, Aulakh R, Bhalla AK, Suri D, Manojkumar R, Narula N, *et al*. Is Kawasaki disease incidence rising in Chandigarh, North India? Arch Dis Child 2011;96:137-40.
24. Rodó X, Ballester J, Cayan D, Melish ME, Nakamura Y, Uehara R, *et al*. Association of Kawasaki disease with tropospheric wind patterns. Sci Rep 2011;1:152.
25. Burns JC, Herzog L, Fabri O, Tremoulet AH, Rodó X, Uehara R, *et al*. Seasonality of Kawasaki disease: A global perspective. PloS One 2013;8:e74529.
26. Onouchi Y, Gunji T, Burns JC, Shimizu C, Newburger JW, Yashiro M, *et al*. ITPKC functional polymorphism associated with Kawasaki disease susceptibility and formation of coronary artery aneurysms. Nat Genet 2008;40:35-42.
27. Matsubara K, Fukaya T. The role of superantigens of group A Streptococcus and *Staphylococcus aureus* in Kawasaki disease. Curr Opin Infect Dis 2007;20:298-303.
28. Kikuta H, Sakiyama Y, Matsumoto S, Hamada I, Yazaki M, Iwaki T, *et al*. Detection of Epstein-Barr virus DNA in cardiac and aortic tissues from chronic, active Epstein-Barr virus infection associated with Kawasaki disease-like coronary artery aneurysms. J Pediatr 1993;123:90-2.
29. Esper F, Shapiro ED, Weibel C. Association between a novel human coronavirus and Kawasaki disease. J Infect Dis 2005;191:499-502.
30. Holm JM, Hansen LK, Oxhoj H. Kawasaki disease associated with parvovirus B19 infection. Eur J Pediatr 1995;154:633-4.
31. Abe J, Kotzin BL, Jujo K, Melish ME, Glode MP, Kohsaka T, *et al*. Selective expansion of T cells expressing T-cell receptor variable regions V beta 2 and V beta 8 in Kawasaki disease. Proc Natl Acad Sci U S A 1992;89:4066-70.
32. Leung DY. Superantigens related to Kawasaki syndrome. Springer Semin Immunopathol 1996;17:385-96.
33. Leung DYM, Meissner HC, Fulton DR, Murray DL, Kotzin BL, Schlievert PM. Toxic shock syndrome toxin-secreting *Staphylococcus aureus* in Kawasaki syndrome. Lancet 1993;342:1385-8.
34. Naoe S, Takahashi K, Masuda H, Tanaka N. Kawasaki disease. With particular emphasis on arterial lesions. Acta Pathol Jpn 1991;41:785-97.
35. Rowley AH, Eckerley CA, Jack HM, Shulman ST, Baker SC. IgA plasma cells in vascular tissue of patients with Kawasaki syndrome. J Immunol 1997;159:5946-55.
36. Rowley AH, Shulman ST, Spike BT, Mask CA, Baker SC. Oligoclonal IgA response in the vascular wall in acute Kawasaki disease. J Immunol 2001;166:1334-43.
37. Tanaka N, Sekimoto K, Naoe S. Kawasaki disease. Relationship with infantile periarteritis nodosa. Arch Pathol Lab Med 1976;100:81-6.
38. Taubert KA, Rowley AH, Shulman ST. Nationwide survey of Kawasaki disease and acute rheumatic fever. J Pediatr 1991;119:279-82.
39. Sato N, Sagawa K, Sasaguri Y, Inoue O, Kato H. Immunopathology and cytokine detection in the skin lesions of patients with Kawasaki disease. J Pediatr 1993;122:198-203.
40. Yanagawa H, Nakamura Y, Yashiro M, Ojima T, Tanihara S, Oki I, *et al*. Results of the nationwide epidemiologic survey of Kawasaki disease in 1995 and 1996 in Japan. Pediatrics 1998;102:E65.
41. Burns JC, Newburger JW. Genetics insights in to the pathogenesis of Kawasaki disease. Circ Cardiovasc Genet 2012;5:277-8.
42. Son MB, Newburger JW. Kawasaki disease. In: Kliegman, Stanton, St. Geme, Schor, Behrman A, Editors. Nelson Textbook of Pediatrics. 19th ed. Philadelphia: Elsevier Saunders; 2011. p. 862-7.
43. Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, *et al*. Diagnosis, treatment and long-term management of Kawasaki disease. Circulation 2004;110:2747-71.
44. Haddock ES, Calame A, Shimizu C, Tremoulet AH, Burns JC, Tom WL. Psoriasiform eruptions during Kawasaki disease (KD): A distinct phenotype. J Am Acad Dermatol 2016;75:6976.
45. Liao YC, Lee JY. Psoriasis in a 3 month old infant with Kawasaki disease. Dermatol Online J 2009;15:10.
46. Brosius CL, Newburger JW, Burns JC, Hojnowski-Diaz P, Zierler S, Leung DY. Increased prevalence of atopic dermatitis in Kawasaki disease. Pediatr Infect Dis J 1988;7:863-6.
47. Vierucci F, Tuoni C, Moscuzza F, Saggese G, Consolini R. Erythema multiforme as first sign of incomplete Kawasaki disease. Ital J Pediatr 2013;39:11.
48. Uehara R, Belay ED. Epidemiology of Kawasaki disease in Asia, Europe, and the United States. J Epidemiol Jpn Epidemiol Assoc 2012;22:79-85.

49. Kumar RK, Tandon R. Rheumatic fever & rheumatic heart disease: The last 50 years. Indian J Med Res 2013;137:643-58.
50. Dahdah N. Not Just Coronary Arteritis, Kawasaki Disease Is a Myocarditis, Too. J Am Coll Cardiol 2010;55:1507
51. Kanegaye JT, Wilder MS, Molkara D, Frazer JR, PancheriJ, Tremoulet AH, *et al*. Recognition of a Kawasaki disease shock syndrome. Pediatrics 2009;123:e783-89.
52. Kato H, Sugimura T, Akagi T, Sato N, Hashino K, Maeno Y, *et al*. Long-term consequences of Kawasaki disease. A 10- to 21-year follow-up study of 594 patients. Circulation 1996;94:1379-85.
53. Gordon JB, Kahn AM, Burns JC. When children with Kawasaki disease grow up: Myocardial and vascular complications in adulthood. J Am Coll Cardiol 2009;54:1911-20.
54. Ghelani SJ, Singh S, Manojkumar R. Endothelial dysfunction in a cohort of North Indian children with Kawasaki disease without overt coronary artery involvement. J Cardiol 2009;53:226-31.
55. Ghelani SJ, Singh S, Manojkumar R. QT interval dispersion in North Indian children with Kawasaki disease without overt coronary artery abnormalities. Rheumatol Int 2011;31:301-5.
56. Gupta A, Singh S, Gupta A, Suri D, Rohit M. Aortic stiffness studies in children with Kawasaki disease: Preliminary results from a follow-up study from North India. Rheumatol Int 2014;34:1427-32.
57. Ghosh A, Chakrabartty S, Niyogi P, Bhattacharyya A. Kawasaki disease with palatal palsy. Indian Pediatr 2000;37:1266-8.
58. Vijayalakshmi AM, Gomathi V. Incomplete Kawasaki syndrome in an eighty-days-old infant. Indian Pediatr 2002;39:485-8.
59. Mitra S, Singh S, Grover A, Kumar L. A child with prolonged pyrexia and peripheral desquamation: Is it Kawasaki Disease? Indian Pediatr 2000;37:786-9.
60. Singh S, Agarwal S, Bhattad S, Gupta A, Suri D, Rawat A, *et al*. Kawasaki disease in infants below 6 months: A clinical conundrum?. Int J Rheum Dis 2016 [Epub ahead of print].
61. Fraison JB, Sève P, Dauphin C, Mahr A, Gomard Mennesson E, Varron L, *et al*. Kawasaki disease in adults: Observations in France and literature review. Autoimmun Rev 2016;15:24-9.
62. Hirata S, Nakamura Y, Yanagawa H. Incidence rate of recurrent Kawasaki disease and related risk factors: From the results of nationwide surveys of Kawasaki disease in Japan. Acta Paediatr 2001;90:40-4.
63. Singh S, Sharma A, Jiao F. Kawasaki Disease: Issues in Diagnosis and Treatment-A Developing Country Perspective. Indian J Pediatr 2016;83:140-5.
64. Singh S, Newburger JW, Kuijpers T, Burgner D. Management of Kawasaki disease in resource-limited settings. Pediatr Infect Dis J 2015;34:94-6.
65. Walsh S, Lee HY, Creamer D. Severe Cutaneous Adverse Reactions to Drugs. In: Griffiths C, Barker J, Bleiker T, Chalmers R, Creamer D, Editors. Rook's Textbook of Dermatology. 9th ed. Sussex: Wiley Blackwell; 2016. p. 119.1-119.23.
66. Hay RJ, Jones RM. Bacterial Infections. In: Griffiths C, Barker J, Bleiker T, Chalmers R, Creamer D, Editors. Rook's Textbook of Dermatology. 9th ed. Sussex: Wiley Blackwell; 2016. p. 26.34-26.36.
67. Hay RJ, Jones RM. Bacterial Infections. In: Griffiths C, Barker J, Bleiker T, Chalmers R, Creamer D, Editors. Rook's Textbook of Dermatology. 9th ed. Sussex: Wiley Blackwell; 2016. p. 26.27-26.29.
68. Salo E, Pesonen E, Viikari J. Serum cholesterol levels during and after Kawasaki disease. J Pediatr 1991;119:557-61.
69. Newburger JW, Burns JC, Beiser AS, Loscalzo J. Altered lipid profile after Kawasaki syndrome. Circulation 1991;84:625-31.
70. Mitra A, Singh S, Devidayal, Khullar M. Serum lipids in North Indian children treated for Kawasaki Disease. Int Heart J 2005;46:811-7.
71. Tsujii N, Tsuda E, Kanzaki S, Kurosaki K. Measurements of Coronary Artery Aneurysms Due to Kawasaki Disease by Dual-Source Computed Tomography (DSCT). Pediatr Cardiol 2016;37:442-7.
72. Singh S, Kumar L. Kawasaki disease: Treatment with intravenous immunoglobulin during the acute stage. Indian Pediatr 1996;33:689-92.
73. Newburger JW, Takahashi M, Burns JC. The treatment of Kawasaki syndrome with intravenous gammaglobulin. N Engl J Med 1986;315:341-7.
74. Furusho K, Kamiya T, Nakano H, Kiyosawa N, Shinomiya K, Hayashidera T, *et al*. High-dose intravenous gammaglobulin for Kawasaki disease. Lancet 1984;2:1055-8.
75. Marasini M, Pongiglione G, Gazzolo D, Campelli A, Ribaldone D, Caponnetto S. Late intravenous gamma globulin treatment in infants and children with Kawasaki disease and coronary artery abnormalities. Am J Cardiol 1991;68:796-7.
76. Burns JC, Capparelli EV, Brown JA, Newburger JW, Glode MP. Intravenous gamma-globulin treatment and retreatment in Kawasaki disease. US/Canadian Kawasaki Syndrome Study Group. Pediatr Infect Dis J 1998;17:1144-8.
77. Durongpisitkul K, Soongswang J, Laohaprasitiporn D, Nana A, Prachuabmoh C, Kangkagate C. Immunoglobulin failure and retreatment in Kawasaki disease. Pediatr Cardiol 2003;24:145-8.
78. Wallace CA, French JW, Kahn SJ, Sherry DD. Initial intravenous gammaglobulin treatment failure in Kawasaki disease. Pediatrics 2000;105:E78.
79. Burns JC, Best BM, Mejias A, Mahony L, Fixler DE, Jafri HS, *et al*. Infliximab treatment of intravenous immunoglobulin-resistant Kawasaki disease. J Pediatr 2008;153:833-8.
80. Singh S, Sharma D, Suri D, Gupta A, Rawat A, Rohit MK. Infliximab is the new kid on the block in Kawasaki disease: A single-centre study over 8 years from North India. Clin Exp Rheumatol 2016;34:134-8.
81. Singh S, Bhattad S, Gupta A, Suri D, Rawat A, Rohit M. Mortality in children with Kawasaki disease: 20 years of experience from a tertiary care centre in North India. Clin Exp Rheumatol 2016;34:129-33.
82. Kothur K, Singh S, Sharma Y, Mittal BR. Prospective follow-up cardiac evaluation of children with Kawasaki disease in Northern India using the Japanese echocardiography criteria. J Cardiol 2007;50:299-307.