Review

Kawasaki disease

By Tomisaku KAWASAKI*),†)

Japan Kawasaki Disease Research Center, Tokyo, Japan
(Communicated by Takashi SUGIMURA, M. J. A.)

Abstract: Short history of Kawasaki disease, clinical features (principal symptoms and other significant symptoms or findings), diagnosis, cardiovascular involvement, epidemiology. Pathological features (lesion of vessels and lesion of organs exclusive of vessels), comparison between infantile periarteritis nodosa (IPN)/Kawasaki disease and classic periarteritis nodosa (CPN), etiology, treatment and management of Kawasaki disease are described.

Key words: Kawasaki Disease (KD); acute febrile mucocutaneous lymph node syndrome(MCLS); coronary artery aneurysms; infantile periarteritis nodosa(IPN).

1. Introduction. Kawasaki disease (KD) is an acute febrile multisystem vasculitis of unknown etiology affecting most often children younger than 5 years of age. It is a unique clinical symptom complex characterized by persistent high fever, bilateral conjunctival hyperemia, mucosal changes of the oropharynx, erythematous rash, erythema and indurative edema of the hands and feet, and cervical lymphadenopathy.

Although KD is of a self-limited nature, approximately 20-25% of untreated patients develop coronary artery changes with a range of severity from asymptomatic coronary artery dilatation or aneurysms to giant coronary artery aneurysms with thrombosis, myocardial infarction and sudden death.

Since the disease was first reported in 1967,[1)] significant advances have been made in its clinical, pathological and epidemiological characterization. However, the etiology, pathogenesis, and mechanism of therapeutic effectiveness of intravenous high-dose gammaglobulin (IVGG) in the reduction of coronary artery aneurysm formation remain unknown. KD has a worldwide distribution having been observed in all continents and in all ethnic groups. At present, KD appears to have replaced acute rheumatic fever as the leading cause of acquired heart disease in children in developed countries.

2. Recognition of KD. Ten years after starting my pediatric career at the Japanese Red Cross Central Hospital (now Japanese Red Cross Medical Center) in Tokyo, I examined on January 5, 1961, a 4 year-3 month old boy, with curious clinical symptom-complex I had never experienced. The patient showed high fever of about two weeks duration, marked bilateral conjunctival hyperemia without discharge, reddening dry fissured lips, diffuse redness of the mucous membrane of oral cavity, strawberry-like tongue, left nonpurulent cervical adenopathy, polymorphous erythema on the body and marked redness of palms and soles with indurative edema of hands and feet following desquamation from the fingertips.

During the patient's hospitalization the patient showed Coombs' test**) positive hemolytic anemia with mild jaundice. I considered that these unusual clinical features might be caused by an autoimmune process. These unique clinical signs of the patient made a strong impression on me and I could not forget the symptoms. Seen from the perspective of today, this patient was a typical Kawasaki disease patient. But at that time I was

*) Recipient of the Japan Academy Prize in 1991.

**) Coombs' test: a test using various antisera, usually employed to detect the presence of proteins (usually but not always antibodies) on the surface of red cells.

†) Japan Kawasaki Disease Research Center, Kubo Bldg 6F, Kandasudacho 1-1-1, Chiyoda-ku, Tokyo 101-0041, Japan.

unable to make a diagnosis. When I presented this case at a clinical conference, it was suggested as atypical scarlet fever or mild-type Stevens-Johnson syndrome. But I did not agree with any of the opinions suggested. Finally the case was declared "Diagnosis Unknown." I always wondered what the diagnosis might be.

In February 1962, a case of suspected sepsis was referred to me from a neighboring doctor. When I saw the child in the emergency room, at a glance I realized that the appearance was very similar to the case which I had experienced the previous year. After admitting the child into the hospital and after careful observation, the patient had a similar clinical course as the previous patient except for Coomb's positive hemolytic jaundice. I realized that there were 2 patients with similar unique clinical symptom complexes that did not exist in any medical reference book. From March to September 1962, I was able to see 5 patients who fell into the same category.

In October I presented 7 cases to the Chiba Regional Pediatric Meeting under the title, "Non scarlatiniform Syndrome with Desquamation from the Fingertips". However there was no discussion.

After encountering the second case, I believed that a disease with these unusual clinical symptoms actually existed. Fascinated by the uniqueness of the cases, I was drawn into the search for deeper understanding.

In 1967, I published my original article entitled, "Infantile Acute febrile Muco-cutaneous lymph node syndrome: clinical observations of 50 cases". [in Japanese with English abstract] Jpn. J. Allerg. 1967; **16**: 178-222.[1)]

I received many requests from many pediatricians from all over Japan to send the separate volume and I became aware that similar patients had been experienced all over Japan.

In 2002 my original article was translated into English[2)] and is now available for everyone who is interested in Kawasaki disease. Jane Burns, one of the translators of the article commented that "The description in Japanese by Tomisaku Kawasaki of 50 infants and children suffering from a curious new ailment in Japan in the 1960s has now been translated into English and is available for readers at http://www.pidj.com. It is truly a masterpiece of descriptive clinical writing from the past century. In his exhaustive detailing of every observable aspect of the disease, Kawasaki was part Sherlock Holmes and part Charles Dickens with his sense of mystery and his vivid descriptions of the clinical features of these patients. So careful are the daily observations of his patients that when one reads in the detailed description of the first case that the patient smiled for the first time on the 26th day of his illness, one is convinced that this is an accurate statement".[3)]

3. Clinical features and diagnosis of KD. In the absence of a diagnostic test for KD, the diagnosis is established by the presence of six principal symptoms.

(a). Principal symptoms

1) Fever of unknown etiology persisting for 5 days or more. In general, the patient has remittent or continuous fever ranging from 38˚C to 40˚C but usually with no prodromal symptoms such as cough, sneezing or rhinorrhea. The duration of fever is usually 1-2 weeks in untreated patients. The fever subsides more rapidly when IVGG is administered with aspirin compared with aspirin alone. In KD, the longer the fever continues, the higher the possibility of coronary artery aneurysms. If fever continues for 10 days or more, severe coronary artery lesions are liable to remain. If fever of unknown origin continues for 1 week to 10 days or longer, and if one or two of the principal symptoms are present, then atypical KD can be assumed and IVGG treatment should be considered.
2) Bilateral hyperemia of ocular conjunctivae. Within 2-4 days of onset, bilateral conjunctival injection develops. It is not associated with exudate. Each capillary vessel is clear because of individual capillary dilatation. Conjunctival injection usually subsides within 1-2 weeks but sometimes continues for more than a few weeks. With IVGG treatment, conjunctival injection may improve quickly following treatment.
3) Changes in lips and oral cavity. Changes in lips and oral cavity are characterized by redness, dryness, fissuring, and bleeding of the lips, diffuse erythema of the oropharyngeal mucosa, strawberry-like tongue without vesicles or pseudomembrane formation, aphthae or ulcerations. Redness of the lips may often continue for 2-3 weeks after the disappearance of other symptoms. Bilateral injection of the eyes together with changes in the lips combine to give the characteristic appearance of KD. This appearance can be an important aid to diagnosis.
4) Polymorphous erythema. From the first to the fifth day after the onset of fever, polymorphous erythma appears on the body and/or extremities. The exanthema can present in many forms: an

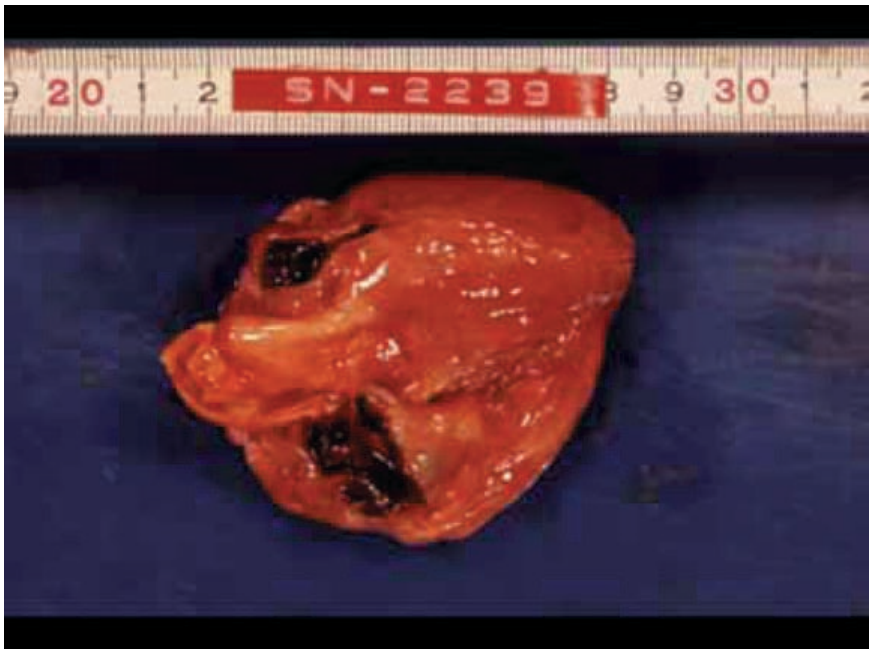


Fig. 1. Autopsied heart of Kawasaki disease: right and left coronary artery aneurysms with thrombosis. (Courtesy of Dr. Tamiko Takemura, Department of Pathology, Japanese Red Cross Medical Center).

urticarial exanthema with large erythematous plaques, a morbillifom maculopapular rash or, in rare cases, erythema multiforme-like with central clearing or iris lesions. In each case, the exanthema is a different combination of these forms. Each lesion becomes increasingly larger, and often lesions coalesce. If the rash shows scarlatiniform erythroderma, careful differentiation is necessary between KD and scarlet fever. There is no vesicle or bullae formation except at the BCG inoculation site. However, about 5% of patients show small, aseptic pustules on the knees, buttocks or other body sites. Desquamation may occur in the perineal region as well as on the hands and feet.

5) Changes in peripheral extremities. The findings on the hands and feet in KD are distinctive. Within 5 days of onset, diffuse erythema of the palms and soles and/or indurative edema of the hands and feet occur. Sometimes the degree of swelling is great and the skin is shiny and looks as though it is about to burst. After the fever subsides, erythema and swelling disappear in most cases. From 10 to 15 days after the onset, there is fissuring between the nails and the tips of the fingers, after which membranous desquamation spreads over the palm up to the wrist in many cases.
6) Acute non-purulant cervical adenopathy. Cervical adenopathy is seen in less than 50% of KD patients in the USA and 60-70% in Japan, whereas the other principal symptoms are each observed in 90% or more of all patients. The size of the swelling ranges from 1.5-5 cm in diameter and in always a firm, non-flucutuant and painful mass. The nodes are usually unilateral. If bilateral adenopathy is seen, it may be misdiagnosed, as mumps. In some patients cervical adenopathy is the most striking clinical symptom of KD, appearing one day before the onset of fever or together with fever.

(b). Other significant symptoms or findings. There are no specific diagnostic laboratory findings in KD. A moderate to marked leukocytosis with a shift to the left, elevation of the erythrocyte sedimentation rate and positive CRP are common. The thrombocytosis in the acute phase of KD ranges from 50×10^4 to 150×10^4 and begins to rise in the second week, peaking at about 3 weeks, but persisting for several months from onset in some cases. This thrombocytosis is a characteristic fea-

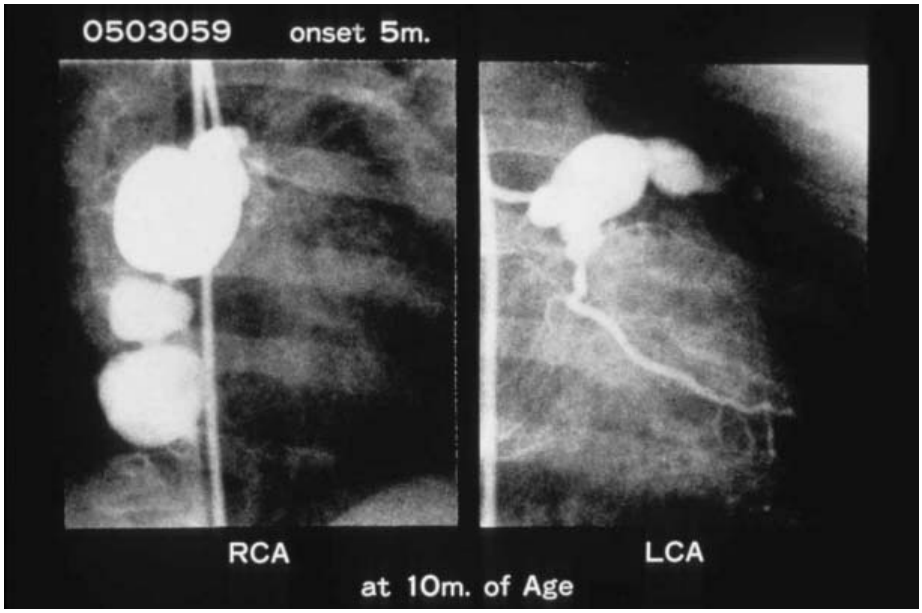


Fig. 2. Angiography of both right and left giant coronary artery aneurysms of Kawasaki disease. (Courtesy of Dr. Atsuko Suzuki, Department of Pediatrics, Tokyo Teishin Hospital).

ture in KD. Aseptic microscopic pyuria is frequently seen in the acute phase in KD and almost always disappears in the convalescent phase. Gastrointestinal complications during the acute phase include abdominal pain, vomiting and diarrhea. Mild jaundice may occur from hydrops of the gallbladder with right upper quadrant abdominal pain. Sometimes there is paralytic ileus and slight increase in serum transaminase levels due to hepatitis. Neurologic symptoms may be seen in the acute phase, including irritability, facial palsy, limb paralysis and febrile convulsion. Loss of consciousness may occur as a result of encephalitis or encephalopathy. Other clinical complications include: arthritis in about 20-30% of cases with involvement of small and large joints, mild proteinuria, occasional aseptic small pustules on the knees, elbows, and/or buttocks, upper respiratory signs such as sneezing and non-productive cough with normal chest radiograph, transverse furrows of the fingernails 2-3 months after onset. There are immunoregulatory abnormalities such as imbalance of T cell population, polyclonal B cell activation, activated monocytes/macrophages and increased cytokines such as TNF-α, INF-γ, IL-1, IL-2, IL-6, interleukin 2 receptors, ICAM-1, etc. However, these cytokines are present in many other disease states that are not associated with the development of arteritis. "It therefore appears that cytokine activation must act in concert with some other unknown mediators of vascular injury." The implications of the described immune abnormalities and cytokine activation for the pathogenesis and treatment of KD are unclear.

(c). Diagnosis. The symptoms of KD can be classified into two categories, principal symptoms and other significant symptoms or findings. For diagnosis of KD, at least five items of 1-6 should be satisfied. However, patients with four items of the principal symptoms can be diagnosed as KD when coronary artery aneurysms or dilatation is recognized by two dimensional echocardiography or coronary angiography.

4. Cardiovascular involvement of KD. The most important clinical problem in KD is cardiovascular lesions, which may cause sudden death or develop into coronary artery disease (Fig. 1).

In the early phase of the illness, pericarditis, myocarditis, endocarditis and coronary arteritis are present and exhibit mild to severe manifestations in most KD patients. In Japan, since 1975,[4),5)] coronary angiography (aortography or selective coronary angiography to evaluate coronary artery aneurysms) were performed (Fig. 2). Since 1979,[6)-8)] usually patients have undergone two-dimensional echocardiography (2DE) which has become the most useful non-invasive method of evaluating coronary aneurysms. Only patients found to have medium to large-sized aneurysms have undergone

Table I. Diagnostic guidelines of Kawasaki Disease

(MCLS: Infantile Acute Febrile Mucocutaneous Lymph Node Syndrome)
(The 5th Revised Edition, February 2002)

This is a disease of unknown etiology affecting most frequently infants and young children under 5 years of age. The symptoms can be classified into two categories, principal symptoms and other significant symptoms or findings.

A. PRINCIPAL SYMPTOMS

1. Fever persisting 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: Reddening of lips, Strawberry tongue, Diffuse injection of oral and pharyngeal mucosa
4. Polymorphous exanthema
5. Changes of peripheral extremities:
   {Initial stage}: Reddening of palms and soles, Indurative edema
   {Convalescent stage}: Membranous desquamation from fingertips
6. Acute nonpurulent cervical lymphadenopathy

At least five items of 1-6 should be satisfied for diagnosis of Kawasaki disease. 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 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-D echo findings (pericardial effusion, coronary aneurysms), Aneurysm of peripheral arteries other than coronary (axillary etc.), Angina pectoris or Myocardial infarction
2. GI tract : Diarrhea, Vomiting, Abdominal pain, Hydrops of gall bladder, Paralytic ileus, Mild jaundice, Slight increase of serum transaminase
3. Blood : Leukocytosis with shift to the left, Thrombocytosis, Increased ESR, Positive CRP, Hypoalbuminemia, Increased α_2-globulin, Slight decrease in erythrocyte and hemoglobin levels
4. Urine : Proteinuria, Increase of leukocytes in urine sediment
5. Skin : Redness and crust at the site of BCG inoculation, Small pustules, Transverse furrows of the finger nails
6. Respiratory : Cough, Rhinorrhea, Abnormal shadow on chest X-ray
7. Joint: Pain, Swelling
8. Neurological : CSF pleocytosis, Convulsion, Unconsciousness, Facial palsy, Paralysis of the extremities

REMARKS :

1. For item 5 under principal symptoms, the convalescent stage is considered important.
2. Non-purulent cervical lymphadenopathy is less frequently encountered (approximately 65%) than other principal symptoms during the acute phase.
3. Male : Female ratio : 1.3 − 1.5 : 1, patients under 5 years of age : 80 − 85%, fatality rate : 0.1%
4. Recurrence rate : 2 − 3%, proportion of siblings cases : 1 − 2%
5. Approximately 10 percent of the total cases do not fulfill five of the six principal symptoms, in which other diseases can be excluded and Kawasaki disease is suspected. In some of these patients coronary artery aneurysms (including so-called coronary artery ectasia) have been confirmed.

coronary angiography (Fig. 2).

According to Kato *et al.*,[9] repeat angiography 5-18 months later in those with abnormalities showed that angiographically regression of the aneurysms occurred within 2 years of onset in about 57% of patients. Among those in whom abnormalities persisted, in one-third the aneurysms disappeared but complete obstruction or marked stenosis of the coronary arteries developed, and in the remainder fine irregularities of the coronary arterial walls without stenosis occurred. If thrombi form in aneurysms, they may increase in size over time and may result in occlusions.

It is clear that coronary artery aneurysms, especially giant aneurysms may result in stenosis of the vessels, and that stenosis often leads to significant coronary obstruction and myocardial ischaemia.

Nakano *et al.*[10] proposed the following quantitative grading system for coronary aneurysms as follows:

Grade 0: normal;
Grade 1: less than 4 mm in diameter (mild);
Grade 2: between 4.0 and 8.0 mm in diameter (moderate);
Grade 3: greater than 8.0 mm in diameter (severe or giant);

Nakano *et al.*[10] suggested that prognosis of aneurysms in Grade 1 and 2 usually may be favorable but in Grade 3 may develop stenosis or occlusion in future.

Sugimura *et al.*[11] were the first to use intravascular ultrasound (IVUS) imaging to evaluate the wall morphology of regressed coronary artery aneurysms in KD patients and concluded that IVUS is useful and could contribute to the assessment of long-term coronary artery sequelae.

5. Epidemiology of KD. In 1970, the KD Research Committee sponsored by the Japanese Government was established. The research committee consisted of epidemiologists, pediatricians, micro-biologists, pathologists etc. The first nation-wide epidemiologic survey was carried out in 1970. The Research Committee compiled the first edition of "Diagnostic Guideline of KD" (Table I and II show the 5th Revised Edition of the Diagnostic Guidelines, the most recent). The guideline was disseminated to hospitals with more than 100 beds and with a pediatric department. A questionnaire was sent to those hospitals with the question of whether or not they had experienced cases according to the guideline.

The Research Committee was able to gather information from around the country on 1,100 cases including more than 20 sudden-death cases. Among them, 10 cases were chosen and the doctors who experienced sudden-death cases were invited to come to Tokyo and to attend a meeting for further discussion. At the meeting, it was found that the clinical features of all cases matched the guideline. Out of 10 cases, 4 cases had been autopsied. All the 4 cases showed right and left coronary artery aneurysms with thrombotic occlusion and the pathological diagnosis was the same as infantile periarteritis nodosa (IPN). At this time the committee became aware that Kawasaki disease was a kind of vasculitic syndrome.

Since then, 17 nationwide surveys[12] (Fig. 3) of KD have been carried out in Japan at two year intervals and a total of 186,069 patients including 419 fatal cases (0.23%) were registered by the end of December, 2002, the largest number throughout the world.[13] Recently, according to a preliminary report of the 18th nationwide epidemiological survey (2003 and 2004) there were 9,000 cases in 2003 and 9,900 cases in 2004. There were three nation-wide epidemics which occurred in 1979, 1982 and 1986. However, there were no epidemics between 1987 and 2004.

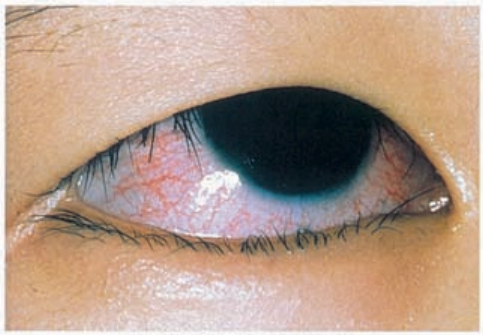
Until 1980 the prevalence of KD among children in the general population less than 4 years of age was less than 50 per 100,000. Since then, this figure has steadily increased: between 1981 and 1993 the annual incidence rose to 70-90 per 100,000, between 1994 and 1999 it increased to more than 100, and between 1994 and 2002 the number jumped from 119.6 to 151.2 per 100,000 (Fig. 4).

The average male-female ratio is 1.4:1. The age distribution shows a peak at between 9 and 11 months of age, 50% of affected children are less than 2 years of age and 80% are less than 4 (Fig. 5). Sibling incidence ranged from 0.7% to 1.4%. The mortality rate was more than 1% until 1974, but fell to 0.1-0.2% between 1974 and 1993. Between 1994 and 2002, the rate was 0.02-0.09% with the exception of 1997 when it was 0.14%. The recurrence rate was 3~4%.

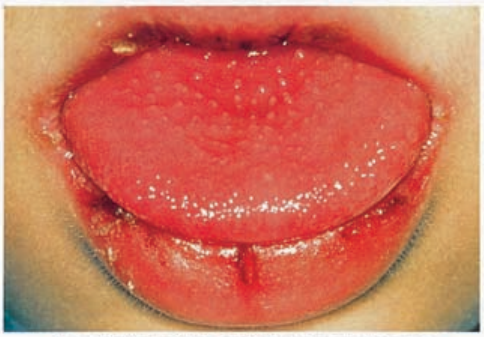
Research in the USA has shown that the incidence of KD is highest among children of Asian extraction and lowest among children of Caucasian extraction. Reports of KD are more numerous from the more industrialized countries than from the developing countries. In 1974, the clinical symptoms and epidemiologic survey results were published in English in *Pediatrics*[14] and drew international attention. Subsequently there have been increased reports on KD from many countries especially from the USA.[15),16)]

In 2002, "A Bibliography of Kawasaki Disease

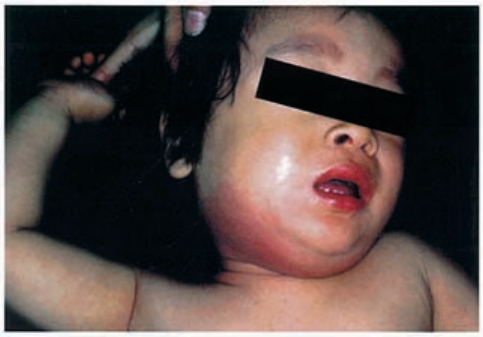
Table II. Characteristic clinical features



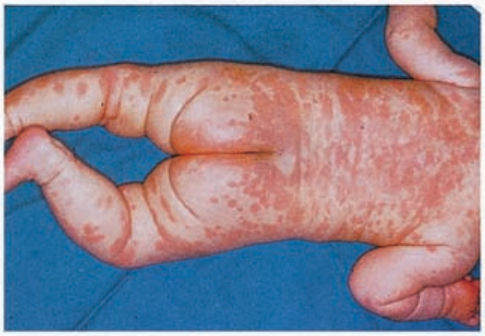
Conjunctival congestion



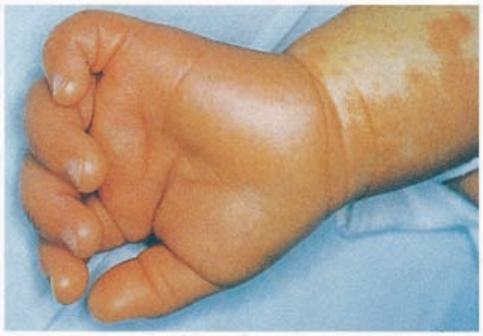
Reddening of lips and strawberry tongue



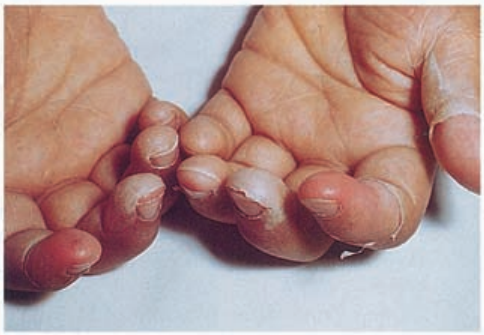
Cervical lymphadenopathy



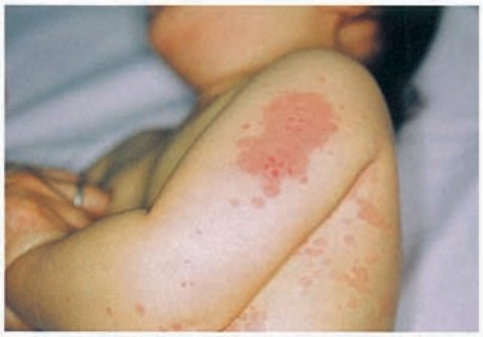
Exanthema



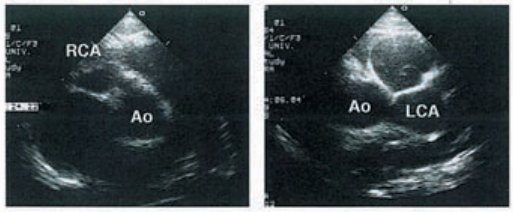
Reddening of hands



Membranous desquamation (Convalescent stage)



Redness at the site of BCG inoculation



Echocardiograms of coronary aneurysms
(Ao: aorta, RCA: right coronary artery, LCA: left coronary artery)

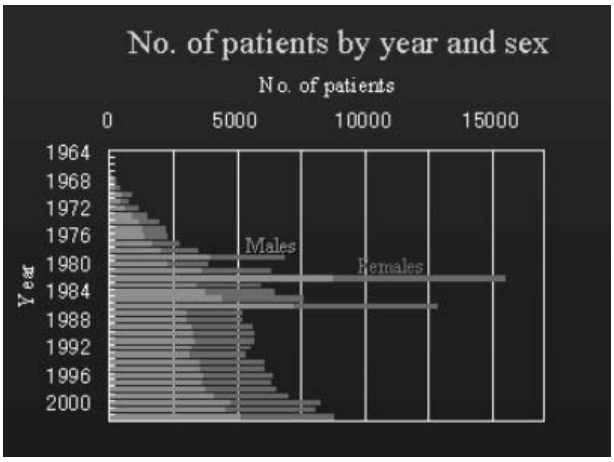


Fig. 3. Number of patients by year and sex.

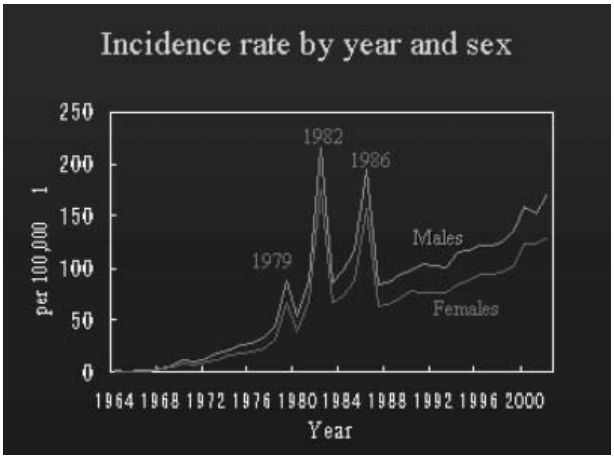


Fig. 4. Incidence rate by year and sex.

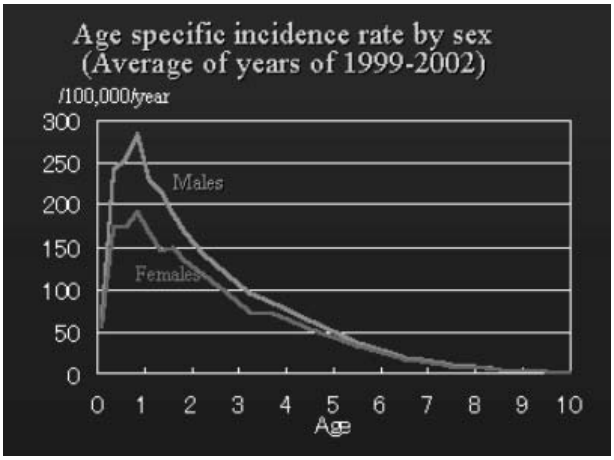


Fig. 5. Age specific incidence by sex (Average of years of 1999-2002).

2002" was published under the editorship of Drs. Yanagawa and Nakamura. There are a total of 5,957 entries, not only in Japanese but also in English and in other languages.[17]

6. Pathological features of KD.

(a) Lesion of vessels.

There have been three Kawasaki disease pathologic research groups with access to a large series of patients. The first is the Tanaka group,[18] the second is the Hamashima group and the third is the Landing group. According to Amano *et al.* in 1979,[19),20] the arterial lesions of KD were categorized with regard to the degree of inflammatory changes and to the duration of the disease. They are divided into six characteristic types of lesions identified in the arterial system.

Type one is endothelial degeneration and increased vascular permeability. Type two is edema and degeneration of the media. Type three is necrotizing panarteritis. Type four is granulation formation. Type five is scar formation. Type six is aneurysm formation.

Aneurysm formation in the coronary artery was present in 94.6% of autopsied cases.

These six types of arteritic changes were not equally distributed throughout the entire arterial system.

Severe lesion such as necrotizing panarteritis was usually localized in arteries such as the main coronary, the iliac, mesenteric and renal arteries which directly branched from the aorta.

It was characteristic that these six types of lesions were simultaneously observed not only in various areas of the arterial tree in the same patient, but also in different portions of one artery.

Inflammatory lesions were also observed in the venous as well as arterial system. Multiple thrombophlebitis was present in small veins in patients who died in the early phase of the disease. Middle sized veins showed, in general, mild lymphocytic infiltration with edema in the media. Panphlebitis was also present in the larger veins such as the main coronary vein, vena cava inferior, vena portae or mesenteric vein in the patients who died within four weeks of onset.

It is thought that the whole process of vasculitis in KD takes about eight weeks.

From general concept of pathomorphology on inflammatory development and its healing process, it is evident that arterial changes in the five types of lesions, progress from the lesion of type one to that of type five. Therefore, these five types of lesions could be classified into five stages from the view point of morphogenesis of arteritis.

Amano *et al*. in 1979 described vascular changes seen in a patient who died immediately after the onset and they observed that vascular changes in this case can be regarded as the early lesion of arteritis. In the endothelial cells of the damaged artery in this patient, not only regressive changes such as degeneration, desquamation or necrosis, but also progressive changes such as hypertrophy or proliferation were observed. The latter changes are considered to be the regeneration of the endothelial cells following injury. Directly beneath the area of the injured endothelial cells, the subendothelial space was edematous and the internal elastic lamina was swollen and acidophilic.

Extraordinary thrombocytosis has been observed in hematological examinations and platelet adhesion or minute platelet thrombus was detected by the histopathologic study of Amano *et al*. in 1979. Extensive injury of the endothelial cells may play a role in aggregation or thrombogenesis of platelets at the damaged areas. A permeability facilitating agent probably takes part in acceleration of the edematous changes. Increased platelets may also play some role in the development of the proliferative change in arterial lesions. The drainage disturbance due to perivascular lymphangitis may accelerate the edematous change due to increased vascular permeability from the intimal side.

Such middle sized arteries are prone to inflammatory invasion from both sides, from the intima with endoarteritis and the perivascular portion with periarteritis. The process may appear to begin in either the adventitia or the intima and penetrate the media. These processes probably induce a florid vascular lesion in the entire vascular wall of the middle sized arteries. When the destructive inflammatory attack exceeds the healing process such as granulation and scar formation, dilatation of the vascular lumen and aneurysm formation develop unable to resist the arterial blood pressure due to marked necrosis of the arterial wall. Extensive splitting or fragmentation of the internal elastic lamina seems to be particularly important for the developmental mechanism of the aneurysm formation. Various degrees of phlebitis were present in the venous system as well as in the arterial system. Therefore, Amano *et al*. conclude that the vascular lesions of KD should be termed systemic vasculitis rather than systemic arteritis.

Fujiwara and Hamashima in 1978[21] have analyzed the arteritis in four stages, with general relation of the stage of the process to the time from onset of illness, as follows: Stage I (zero to nine days) was characterized by acute perivasculitis and vasculitis of the microvessels (arterioles, capillaries and venules) and small arteries, and acute perivasculitis and endoarteritis of the three MCAs (major coronary arteries). Pericarditis, myocarditis, inflammation of the atrioventricular conduction system, and endocarditis with valvutitis were also present.

Stage II (12 to 25 days) was characterized by panvasculitis of the MCAs and aneurysm with thrombus in the stems. Myocarditis, coagulation necrosis, lesion of the conduction system, pericarditis, and endocarditis with valvulitis were also present.

Stage III (28 to 31 days) was characterized by granulation of the MCAs and disappearence of inflammation in the microvessels were noted.

Stage IV (40 days to 4 years) was characterized by scarring with severe stenosis in the MCAs. Fibrosis of the myocardium, coagulation necrosis, lesions of the conduction system, and endocardial fibroelastosis were also seen.

The features observed revealed KD to be acute and inflammatory. The angiitis begins in the microvessels and fibrinoid necrosis of the media is rare.

Kyogoku in 1987[22] has written that, most cases last about eight weeks and are of one process without stages and he has called the process the 'one hit' type with little recurrence.

Landing and Larson in 1977[23] and 1987[24] divided arterial changes of KD into early (active) and later (fibrosing) lesions in autopsy material. In cases "less than two weeks" and 'four weeks of illness', there were both early and late arterial lesions. Early lesions were more prominent than late lesions but both existed. At five weeks, early and late lesions were of equal proportions. In cases longer than six weeks, late lesions were more prominent than early ones. After four months, early lesions were rare.

In order to explain the presence of early and late lesions together at the very early stage of the disease, Landing and Larson proposed that before clinical manifestations appeared, there must have been a period of subclinical lesions before the appearance of symptoms. They suspect that there is a clinically inapparent episode.

Such a course could explain the surprisingly high proportion of later stage vascular lesions found in those patients reviewed who died within two weeks of onset of acute disease. Landing and Larson have proposed several possible situations: (a) a single clinically apparent

episode followed by a second episode not clinically recognized, (b) two episodes of acute process, neither one clinically apparent, (c) a clinically apparent episode followed after a brief period of clinical improvement, by a second clinical episode. (Patients with KD who have a 'camel-back' clinical course are thought to have a poorer prognosis than those with only one episode of acute stage signs and symptoms), (d) a clinically inapparent acute stage followed by a second, clinically apparent episode, (e) two episodes of acute process, neither one clinically apparent.

Most KD patients seem to have a clinically apparent course of a single episode. However, Landing and Larson's analyses based on clinical observation and autopsied materials are a reasonable conclusion to explain those seemingly clinically inexplicable recrudescence cases.

Recent conception is that the term IPN (infantile periarteritis nodosa) is inadequate to describe fatal KD cases. IPN is different from CPN (classic periarteritis nodosa) or adult PN and that a more accurate description for IPN would be infantile polyarteritis or juvenile polyvasculitis. KD autopsy cases, pathologically, could be described as infantile polyarteritis or juvenile polyvasculitis.

(b) Lesions of organs exclusive of vessels.

Lesions other than those in the vessels are seen when there is myocarditis (interstitial myocarditis with mild necrosis) involving conduction system, pericarditis, and endocarditis. Also, cholecystitis, cholangitis, pancreatic ductitis, sialoadenitis, meningitis and lymphadenitis are frequently seen.

Pathologic changes are also noted in the intestines, liver, pancreas, lungs, bronchi, kidneys, ganglion, spleen, thymus, prostata, fatty tissue and muscle.

All these lesions are frequently seen in stage I and II (Fujiwara and Hamashima in 1978[21]) but rarely in stage IV. Ischemic heart disease occurs in stages II to IV. Acute myocardial infarction may not be histologically detectable in some autopsied cases. When sudden death cases are autopsied immediately, arterial obstruction can be seen but myocardial lesions such as necrosis have not yet had time to occur.

Among ischemic heart disease cases there is fibrosis and/or necrosis of over one third of the thickness of the left ventricular wall, with marked stenosis or obstruction of the major coronary arteries. These changes are probably due to residual myocardial infarction rather than to myocarditis.

The major causes of death in each stage are as follows: in stage I the major cause is myocarditis, including inflammation of the AV (atrioventricular) conduction system. In stage II and III the major causes are ischemic heart disease, rupture of aneurysm (rare) and myocarditis. In stage IV the major cause of death is also ischemic heart disease.

(c) Comparison between IPN/KD and CPN.

Tanaka *et al*. in 1976,[18] and Landing and Larson in 1977[23] described that pathologically and clinically IPN could not be differentiated from fatal KD. On the other hand, Landing and Larson also described that CPN typically causes petechial or purpuric rash (with vasculitis often demonstrable by skin biopsy), typically produces a more protracted acute phase of illness, and causes more severe nephritic features, with renal insufficiency, than does IPN/KD, and produces more extensive fibrinoid necrosis of vessel walls. Typically, CPN produces more extensive intramural involvement of the gastrointestinal tract. If coronary arteries are affected, CPN involves medium and small vessels rather than main coronary arteries. CPN typically involves arteritis of skeletal muscles. CPN is seen in persons older than those affected by IPN/KD.

CPN is a progressive and recurrent inflammatory disease but KD is not (Fujiwara and Hamashima in 1978.[21]

7. Etiology of KD. Up to now, many hypotheses have been proposed regarding the etiology of KD, but nothing has been confirmed by other investigators. Among these, the theory involving retroviruses proposed in 1986 by doctors of three children's hospitals in the USA (Boston,[25] Chicago,[26] and Honolulu[27]) has attracted attention.

A cooperative study to confirm the retrovirus theory, conducted by the Japanese Kawasaki Disease Research Group of the Ministry of Health and Welfare in cooperation with leading Japanese institutions including the Institute of Virology at Kyoto University, the Institute of Microbiology at Osaka University and the Department of Virology of the National Cancer Center,[28] showed negative results.

Various immunological abnormalities[29)-35)] have been reported to be associated with KD, but no consistent results have yet been obtained. Thus, the true profile of immunological changes associated with the disease remain unclear. Further progress in medical science, such as etiological microbiology, immunology and genetics, should eventually clarify the etiology and pathogenesis.

8. Treatment and management of KD. The

most effective treatment in the acute stage of KD is IVGG plus aspirin, which produces a rapid reduction in fever and coronary artery changes.

The original IVGG regimen, 400 mg/kg/day for 5 days, was established by Furusho *et al*.[36] in 1984 and until 1991 was the principal treatment regimen internationally. However, the new IVGG regimen, 2 gr/kg/day in one infusion was established in 1991 by the American Multi-Center Collaborative Controlled Trial,[37] and results are reported to be better than with Furusho's regimen. At present, this regiment is the main international standard regimen.

Aspirin is also administered in a low dose of 30-50 mg/kg/day in Japan, but in a high dose of 80-100 mg/kg/day in the USA because of difference of sensitivity to aspirin. In both Japan and the USA, once fever subsides, the aspirin dosage is reduced to 3-5 mg/kg/day and continued for 2 months.

Early diagnosis and treatment are important. If KD can be diagnosed within 1 week of onset and if IVGG treatment can be started early, coronary artery changes would be prevented in less than 5% of all patients. There are still 10-15% of cases resisting IVGG in the lowering of fever and need retreatment.[38),39] However, giant aneurysms in a few patients (0.4%) have developed despite the fact that IVGG treatment was started within 7 days of onset. If diagnosis is delayed until 10 or more days after onset, the risk of coronary artery changes rapidly increases.

In patients with coronary artery changes, prognosis depends on the size of the aneurysms. Small aneurysms (less than 4 mm in diameter) usually undergo natural regression within 1 year and prognosis is good. Medium-sized aneurysms (4-8 mm in diameter) undergo regression within 2 years in more than one-half of cases. In some remaining cases, stenosis and obstruction may develop despite continued anticoagulant treatment. In patients with giant aneurysms, provided high-dose anticoagulant treatment is continued, obstruction, if it develops, will do so only gradually. The younger the child, the more likely it is that ischemia will result in collateral circulation. Thus, even if there is complete obstruction, myocardial infarction is asymptomatic. In patients in whom asymptomatic myocardial infarction is suspected, ^{201}TI scintigraphy or myocardial imaging should be performed.

Some patients with ventricular dysfunction, heart failure, severe arrhythmias or postinfarction angina are managed by catheter intervention[40] and/or surgical treatment. According to Kitamura *et al*.,[41] 168 patients with KD in Japan have undergone bypass surgery. Bypass grafting using the intrathoratic artery for left coronary artery and the gastroepiploic artery for right coronary artery are recommended because the long-term patency with arterial grafts is much higher than with a saphenous vein graft.

9. Conclusion. More than 35 years have passed since Kawasaki's original paper was published in 1967. It is clear that there are KD patients not only in Japan but in countries all over the world. There has been much progress in treatment due to IVGG treatment which can prevent coronary artery changes in most cases. However the etiology and pathogenesis remain unknown.

The ultimate aim of clinical medicine is prevention. In order to prevent KD, the etiology must become clear. Clinicians and basic scientists working together are aiming to discover the etiology.

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References

1) Kawasaki, T. (1967) Infantile acute febrile mucocutaneous lymph node syndrome with specific desquamation of the fingers and toes. Clinical observation of 50 cases. Jpn. J. Allerg. **16**, 178-222 (in Japanese with English abstract).
2) Burns, J. C. (2002) Commentary: Translation of Dr. Tomisaku Kawasaki's original report of fifty patients in 1967. Pediatr. Infect. Dis. J. **21**, 993-995.
3) Shike, H., Shimizu, C., and Burns, J. C. (2002) Translation of Dr. Tomisaku Kawasaki original report of fifty patients in 1967 (Available at http//www.pidj.com).
4) Kato, H., Koike, S., Yamamoto, M., Ito, Y., and Yano, E. (1975) Coronary aneurysms in infants and young children with acute febrile mucocutaneous lymph node syndrome. J. Pediatr. **86**, 892-898.
5) Onouchi, Z., Tomizawa, N., Goto, M., Nakata, K., and Fukuda, M. (1975) Cardiac involvement and prognosis in acute mucocutaneous lymph node syndrome. Chest **68**, 297-301.
6) Yoshikawa, J., Yanagihara, K., Owaki, T., Kato, H., Takagi, Y., Okumachi, F., Fukaya, T., Tomita, Y., and Baba, K. (1979) Cross-sectional echocardiographic diagnosis of coronary artery aneurysms in patients with the mucocutaneous lymph node syndrome. Circulation **59**, 133-139.
7) Hiraishi, S., Yashiro, K., and Kusano, S. (1979) Noninvasive visualization of coronary arterial aneurysm in infants and

young children with mucocutaneous lymph node syndrome with two dimensional echocardiography. Am. J. Cardiol. **43**, 1225-1233.

8) Yoshida, H., Funabashi, T., Nakaya, S., and Taniguchi, N. (1979) Mucocutaneous lymph node syndrome. A cross-sectional echocardiographic diagnosis of coronary aneurysms. Am. J. Dis. Child. **133**, 1244-1247.
9) Kato, H., Ichinose, E., Yoshioka, F., Takechi, T., Matsunaga, S., Suzuki, K., and Rikitake, N. (1982) Fate of coronary aneurysms in Kawasaki disease: serial coronary angiography and long-term follow-up study. Am. J. Cardiol. **49**, 1758-1766.
10) Nakano, H., Ueda, K., Saito, A., and Nojima, K. (1983) Repeated quantitative angiograms in coronary arterial aneurysm in Kawasaki disease. Am. J. Cardiol. **56**, 846-851.
11) Sugimura, T., Kato, H., Inoue, O., Fukuda, T., Sato, N., Ishii, M., Takagi, J., Akagi, T., Maeno, Y., and Kawano, T. (1999) Intravascular ultrasound of coronary arteries in children. Assessment of the wall morphology and the lumen after Kawasaki disease. Circulation **89**, 258-265.
12) Nakamura, K., Yashiro, M., Uehara, R., and Yanagawa, H. (2004) Results of the 17th nationwide epidemiological survey of Kawasaki disease in Japan. Shonika Shinryo **67**, 313-323 (in Japanese).
13) Yanagawa, H., Nakamura, Y., Yashiro, M., and Kawasaki, T. (eds.) (2004) Epidemiology of Kawasaki Disease. 30-Year Achievement. Shindan-to-Shinryosha, Ltd., Tokyo.
14) Kawasaki, T., Kosaki, F., Okawa, S., Shigematsu, I., and Yanagawa, H. (1974) A new infantile acute febrile mucocutaneous lymph node syndrome (MLNS) prevailing in Japan. Pediatrics **54**, 271-276.
15) Taubert, K. A., Rowley, A. H., and Shulman, S. T. (1991) Nationwide survey of Kawasaki disease and acute rheumatic fever. J. Pediatr. **119**, 279-282.
16) Taubert, K. A. (1997) Epidemiology of Kawasaki disease in the United States and worldwide. Prog. Pediatr. Cardiol. **6**, 181-185.
17) Nakamura, Y., Hasegawa, H., Yanagawa, H., and Kawasaki, T. (eds.) (2002) A Bibliography of Kawasaki Disease 2002 Japan Kawasaki Disease Research Center, Tokyo.
18) Tanaka, N., Sekimoto, K., and Naoe, S. (1976) Kawasaki disease. Relationship with infantile periarteritis nodosa. Arch. Pathol. Lab. Med. **100**, 81-86.
19) Amano, S., Hazama, F., and Hamashima, Y. (1979) Pathology of Kawasaki disease I. Pathology and morphogenesis of the vascular changes. Jpn. Circ. J. **43**, 633-643.
20) Amano, S., Hazama, F., and Hamashima, Y. (1979) Pathology of Kawasaki disease II. Distribution and incidence of the vascular changes. Jpn. Circ. J. **43**, 741-748.
21) Fujiwara, H., and Hamashima, Y. (1978) Pathology of the heart in Kawasaki disease. Pediatrics **61**, 100-107.
22) Kyogoku, M. (1987) A pathological analysis of Kawasaki disease-with some suggestions of its etio-pathogenesis. *In* Kawasaki Disease. Progress in Clinical and Biological Research (ed. Shulman, S. T.). Alan Liss, New York, pp. 267-273.
23) Landing, B. H., and Larson, E. J. (1977) Are infantile periarteritis nodosa with coronary artery involvement and fatal mucocutaneous lymph node syndrome the same? Comparison of 20 patients from North America with patients from Hawaii and Japan. Pediatrics **59**, 651-662.
24) Landing, B. H., and Larson, E. J. (1987) Pathological features of Kawasaki disease (mucocutaneous lymph node syndrome). Amer. J. Cardiovasc. Pathol. **1**, 218-229.
25) Burns, J. C., Geha, R. S., Schneeberger, E. E., Newburger, J. W., Rosen, F. S., Glezen, L. S., Huang, A. S., Natale, J., and Leung, D. Y. (1986) Polymerase activity in lymphocyte culture supernatants from patients with Kawasaki disease. Nature **323**, 814-816.
26) Shulman, S. T., and Rowley, A. H. (1986) Does Kawasaki disease have a retroviral aetiology? Lancet, 545-546.
27) Melish, M. E., Marchette, N. J., Kaplan, J. C., Kihara, S., Ching, D., and Ho, D. D. (1988) Absence of significant RNA-dependent DNA polymerase activity in lymphocyte cultures from patients with Kawasaki disease. Proceedings of the third International Kawasaki disease symposium. Japan Heart Foundation, Tokyo, pp. 76-83.
28) Okamoto, T., Kuwabara, H., Shimotohno, K., Sugimura, T., Yanase, Y., and Kawasaki, T. (1988) Lack of evidence of retroviral involvement in Kawasaki disease. Pediatrics **81**, 599.
29) Furukawa, S., Matsubara, T., Jujoh, K., Yone, K., Sugawara, T., Sasai, K., Kato, H., and Yabuta, K. (1988) Peripheral blood monocyte/macrophages and serum tumor necrosis factor in Kawasaki disease. Clin. Immunol. Immunopathol. **48**, 247-251.
30) Maury, C. P., Salo, E., and Pelkonen, P. (1988) Circulating interleukin-1β in patients with Kawasaki disease. N. Engl. J. Med. **319**, 1670-1671.
31) Furukawa, S., Imai, K., Matsubara, T., Yone, K., Yachi, A., Okumura, K., and Yabuta, K. (1992) Increased levels of circulating intercellular adhesion molecule 1 in Kawasaki disease. Arthritis Rheum **35**, 672-677.
32) Abe, J., Kotzin, B. L., Jujo, K., Melish, M. E., Glode, M. P., Kohsaka, T., and Leung, D. Y. (1992) Selective expansion of T cells expressing T-cell receptor variable regions Vβ2 and Vβ8 in Kawasaki disease. Proc. Natl. Acad. Sci. USA **89**, 4066-4070.
33) Yoshioka, T., Matsutani, T., Iwagami, S., Toyosaki-Maeda, T., Yutsudo, T., Tsuruta, Y., Suzuki, H., Uemura, S., Takeuchi, T., Koike, M., and Suzuki, R. (1999) Polyclonal expansion of TCRBV2- and TCRBV6-bearing T cells in patients with Kawasaki disease. Immunology **96**, 465-472.
34) Rowley, A. H., Baker, S. C., Shulman, S. T., Garcia, F. L., Guzman-Cottrill, J. A., Chou, P., Terai, M., Kawasaki, T., Kalelkar, M. B., and Crawford, S. E. (2004) Detection of antigen in bronchial epithelium and macrophages in acute Kawasaki disease by use of synthetic antibody. J. Infect. Dis. **190**, 856-865.
35) Matsubara, T., Ichiyama, T., and Furukawa, S. (2005)

Immunological profile of peripheral blood lymphocytes and monocytes/macrophages in Kawasaki disease. Clin. Exp. Immunol. **141**, 381-387.

36) Furusho, K., Kamiya, T., Nakano, H., Kiyosawa, N., Shinomiya, K., Hayashidera, T., Tamura, T., Hirose, O., Manabe, Y., Yokoyama, T. *et al*. (1984) High-dose intravenous gammaglobulin for Kawasaki disease. Lancet 1055-1058.

37) Newburger, J. W., Takahashi, M., Beiser, A. S., Burns, J. C., Bastian, J., Chung, K. J., Colan, S. D., Duffy, C. E., Fulton, D. R., Glode, M. P. *et al*. (1991) A single intravenous infusion of gamma globulin as compared with four infusions in the treatment of acute Kawasaki syndrome. N. Engl. J. Med. **324**, 1633-1639.

38) Hashino, K., Ishii, M., Iemura, M., Akagi, T., and Kato, H. (2001) Re-treatment for immune globulin-resistant Kawasaki disease: a comparative study of additional immune globulin and steroid pulse therapy. Pediatr. Int. **43**, 211-217.

39) Burns, J. C., Mason, W. H., Hauger, S. B., Janai, H., Bastian, J. F., Wohrley, J. D., Balfour, I., Shen, C. A., Michel, E. D., Shulman, S. T., and Melish, M. E. (2005) Infliximab treatment for refractory Kawasaki syndrome. J. Pediatr. **146**, 662-667.

40) Ishii, M., Ueno, T., Ikeda, H., Iemura, M., Sugimura, T., Furui, J., Sugahara, Y., Muta, H., Akagi, T., Nomura, Y. *et al*. (2002) Sequential follow-up results of catheter intervention for coronary artery lesions after Kawasaki disease. Quantitative coronary artery angiography and intravascular ultrasound imaging study. Circulation **105**, 3004-3010.

41) Kitamura, S., Kameda, Y., Seki, T., Kawachi, K., Endo, M., Takeuchi, Y., Kawasaki, T., and Kawashima, Y. (1994) Long-term outcome of myocardial revascularization in patients with Kawasaki coronary artery disease. A multicenter cooperative study. J. Thorac. Cardiovasc. Surg. **107**, 663-674.

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