Professor Tomisaku Kawasaki
A Biographic Tribute and Discovery Chronology

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Dr. Tomisaku Kawasaki

Tomisaku Kawasaki, Born: February 7, 1925 in Tokio Japan

Died– June 5, 2020 Tokio Japan

Discovery Chronology

1961: In the first manuscript he wrote: "I (TK) saw my first case of the disease that is now known as Kawasaki disease (KD) in January 1961, when I was working as staff pediatrician at the Red Cross Hospital in Tokyo". Almost 60 years has passed since Professor Tomisaku Kawasaki's first description of this unique disease, Kawasaki disease (KD). This was a 4-year-old boy who had presented with a febrile exanthem. Dr. Kawasaki described the clinical features and proffered the diagnosis in this child as

“unknown”. This unknown diagnosis later turned out to be an important key to his serendipitous discovery of a new disease entity that was to bear his name. This discovery was based on his deep insight into astute clinical observations and scientific considerations. He reported his cases as a possible new disease at a pediatric meeting at Chiba and Tokyo.

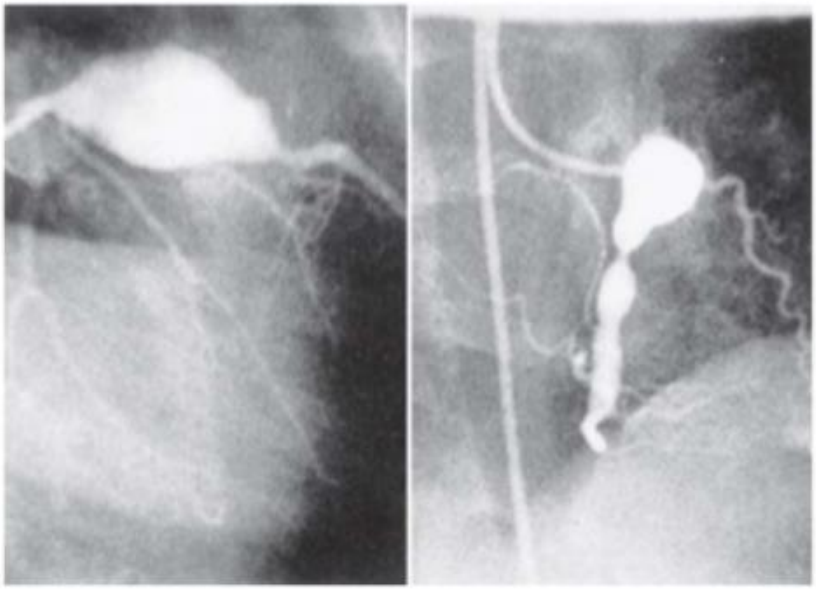
In 1962 After he had collected a series of seven cases, he presented them at a meeting of the Japanese Pediatric Association. These initial presentations met with lot of opposition from his academic peers who thought that what he was describing was nothing other than ‘Still’s disease’ or ‘Stevens–Johnson syndrome’. Reviewers rejected his submission for publication because they did not believe it was a new disease entity**. (1)** However, Dr. Kawasaki had the courage of conviction to stand by his initial observations and he was convinced that this was indeed a new disease entity.

In 1967, He reports a series of 50 patients and establishes the clinical criteria for diagnosis. in the Japanese Journal of Allergy covering 44 pages and had magnificent color illustrations that he had painstakingly collected. This original publication is still considered to be a masterpiece of accurate clinical observations and continues to be cited. **(2)**. Only after he had collected a total of 50 cases his paper was published in 1967. **(3)**

1970: The first set of guidelines or diagnostic criteria of this disease that was published mainly based on this article. However, the cardiac symptoms or findings were not described in this article. The first nationwide survey in Japan reported 10 fatal cases and the pathological findings of all autopsy cases demonstrated coronary aneurysms and thrombotic occlusion. The controversy was resolved by the first Japanese nationwide survey of KD (1970) in which 10 autopsy cases of sudden cardiac death after KD were documented and all of them were found to have significant coronary artery abnormalities It was not until 1970, that the Ministry of Health and Welfare eventually established a research committee on MCLS in 1970. **(4)**

1973, Dr Hirohisa Kato (his disciple) introduced coronary angiography for 20 patients who had recovered from acute KD. Twelve of these patients had multiple coronary aneurysms. This was not only the first description of coronary aneurysms in living

patients but also the first recognition that these aneurysms can exist in children who are completely asymptomatic. **(5)**



Coronary angiogram demonstrating giant aneurism of the left anterior descending coronary artery (LAD) with obstruction and giant aneurism of the right coronary artery (RCA) with an area of sever narrowing in 6yr old boy

In this year, a pathologist discovered the connection to cardiac disease when he found coronary artery thrombosis at an autopsy. **(6)**

1974: He publishes his first article in the English language described detailed clinical findings and epidemiology in Japan, and alluded to a small number of patients who had died from myocardial infarction. **(7)**

1976 First English language teport of Kawasaki syndrome by Melish, Hawaii. Landing and Larson establish that Kawasaki disease and infantile polyarteritis nodosa are pathologically indistinguishable.

1978 The disease was described in Nelson's Textbook of Pediatrics as "mucocutaneous lymph node syndrome" or Kawasaki disease (KD). By this time KD had attracted a lot of

attention in pediatric units the world over, but especially in the USA. The lay press was equally fascinated with this clinical entity that resulted in coronary events in babies and small children that mimicked the complications of adult coronary artery disease. However, at that time it was not easy to assess coronary artery lesions associated with KD. The electrocardiogram was not helpful in diagnosing coronary aneurysms and two-dimensional echocardiography was not available at that time.

1986 American academy of pediatrics endorses high does Intravenous Immunoglobulin (IVIG) plus Acetylsalicylic Acid (ASA) as recommended therapy for KD

KD is identified as the most common vasculitis of childhood and is also the most common cause of acquired heart disease in children in several Asian countries (e.g., Japan, Korea, Taiwan from where accurate nationwide data are available), Europe, North America and Australia. **(8)** Various epidemiologic trends showed that the incidence of KD is increasing in several developing countries as well, as for instance China and India. **(9)** What is of concern to all pediatricians is the fact that coronary artery abnormalities can occur in as many as 15–25% of patients if KD is left undiagnosed and untreated. **(10)** Unfortunately, a significant number of children with KD are still getting missed, especially in developing countries where this condition is often confused with viral exanthemata and other infectious diseases. **(11)** Dr Kawasaki wrote "It has been 50 years since I (TK) published my first series on this condition". The International Journal of Rheumatic Diseases is bringing out a special issue on KD to mark this occasion. This issue begins with the first article entitled 'Tomisaku Kawasaki

– Dr. Hirohisa Kato. **(12)** highlights his concerns about possible long-term cardiac sequelae in these patients even when there are no overt coronary artery abnormalities – an aspect that is still not clearly understood.

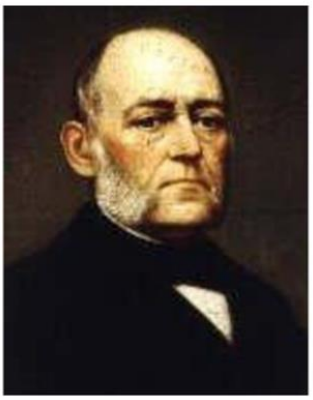
The first reported case of Kawasaki disease?

In her 1949 review for "Fifty Years Ago in The Journal of Pediatrics" by G. C. Fanney, Jr, on Erythema Multiform Exudativum; Stevens-Johnson syndrome **(13)**, she correctly concludes that case No. 5 (who died in 1948 of a ruptured coronary artery aneurysm) actually represented a fatal case of what we today know as Kawasaki disease (KD). **(14)** She asks whether this is the first recorded instance of KD in the United States, an illness first described clinically by Dr Tomisaku Kawasaki in 1967 in Japan. **(3)** Earlier reports

of individual cases of fatal childhood illnesses can be found that surely represent examples of the same illness recognized by Kawasaki (and here by Dr Long); this includes a report in The Journal of Pediatrics. Specific examples include 2 Kentucky girls, a 5-year-old and a 9-month-old, one of whom died of acute coronary rupture and the other of severe coronary arteritis with near-rupture 10 days and 4 weeks, respectively, after onset of an acute illness with features of KD; a 5-year-old New York girl who died in 1939 at Willard Parker Hospital 4 weeks after onset of an illness with KD features and who was found to have a ruptured left coronary aneurysm**(16)**; and a 2-year-old boy who died in Toronto in 1935 about 1 month after onset of an illness with features suggesting acute KD and who was found at autopsy to have severe coronary arteritis with aneurysm formation. **(17)** Additional cases from Europe can be identified, dating back to the 19th century. **(18-19)** Dr Long should be congratulated for her careful review of the 1949 article and for her careful assessment of the cases included in that interesting report

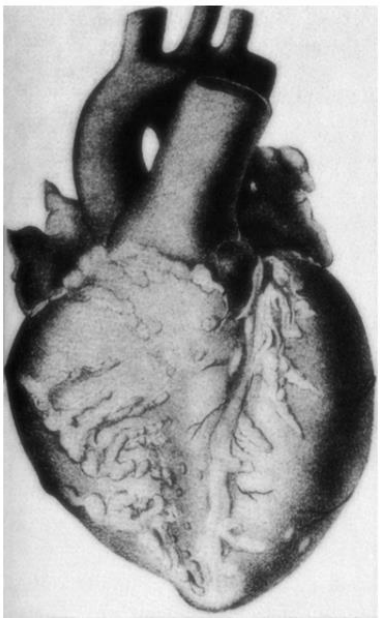
Historical chronology

In the Beginning....



Baron
Carl Freiherr von Rokitansky
19 February 1804 – 23 July 1878

Rosary Sign –Worm etiology



In polyarteritis nodosa, small aneurysms are strung like the beads of a rosary, therefore making "rosary sign" a diagnostic feature of the vasculitis.

Clinical and Pathologic Description Kussmaul and Maier (1866)….

- Adolf Kussmaul – eminent clinician – ophthalmoscope, endoscopy, respiration in DKA
- Kussmaul and Maier describe "periarteritis nodosa" in adults
- ("Kussmaul-Maier Disease")
- Detailed microscopic description
- Arterial dilatation with transmural inflammation described

In 1866 Kussmaul&Maier -described nodular inflammation of muscular arteries termed Peroarteritis nodosa -latter changed to polyarteritis nodosa(PAN)

Pediatric Periarteritis Nodosa in the 20th Century

- In the first half of the 20th century, **pediatric** periarteritis nodosa was recognized and reported as a distinct entity, "a constant clinical syndrome."
- Most cases were diagnosed at autopsy, generally in young children

Keith & Baggenstoss, 1941, Emphasized Coronary Disease in Childhood Periarteritis Nodosa

Covid 19 Connection to Kawasaki Disease SARS-CoV-2 infection in children is usually milder. In Italy, as of 5/8/2020, people were infected by SARS-CoV-2, with less than 2% being under 18 years. Only three pediatric deaths have been reported (https://www.epicentro.iss.it/coronavirus/bollettinoqinfogrfica_8maggio%20ITA,pdf). Systemic hyperinflammation due to SARS-CoV-2 infection is currently considered rare in children. **(20)** The initial case appears to have been a 6- month-old girl with SARS-CoV-2 who presented with conjunctivitis, polymorphous rash, swollen extremities, and persistent fever, This patient was treated as if she had KD with IV immunoglobulin(IVIG) and acetylsalicylic acid, and improved **(21;22)**

COVID 19 is appearing as a trigger to a Kawasaki like syndrome that is causing toxic shock & cardiac arrest in children. Now named as PIMS disorder (Paediatric Inflammatory Multi Organ Syndrome)**.** Over 40 children seen with the condition that presents itself in it's severity affecting all the organs compared to classic KD.

Kawasaki disease is a genetic predisposition triggered when the child comes into contact with an agent causing inflammation & irreversible damage to the heart if not diagnosed within 4 days.

Tomisaku Kawasaki education

Tomisaku Kawasaki was born in Tokyo as the youngest of seven children. He was interested in plants and fruit, and surprised to learn how the 20th-century pear had suddenly appeared, but eventually abandoned plans to study botany because his mother favored him to be a physician.

He studied medicine at Chiba University graduating in 1948. **(23)**

Trajectory

He decided to specialize in pediatrics, because he liked children. **(24)**

Residency then was an unpaid job and after graduation he needed and found a paid position at Tokyo's Japan Red Cross Medical Center in Hiroo. He practiced pediatrics there for most of his life. After 10 years of researching milk allergy and unusual host-parasite cases he saw his first patient with what he termed "acute febrile mucocutaneous lymph node syndrome" (MCLS). **(25)**.

He retired in 1990, and established the Japan Kawasaki Disease Research Center, which he led until 2019.

Personal life and death

Kawasaki was married; his wife preceded him in death in 2019. He was 95 years old in June 2020, when he died of old age.

Awards

- Japan Academy Prize, 1991
- Japan Pediatric Society Prize, 2006
- honored by the Tokyo Metropolitan Government

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