I want to express my sorrow at the loss of Dr. Tomisaku Kawasaki. He gently passed away at 95 years old, surrounded by his family. We will miss a great pediatrician and an outstanding clinical investigator, whose scientific achievements, and my own contact with him, are described in this special issue.

Since the first description of the unique disease, Kawasaki disease, by Dr. Tomisaku Kawasaki almost 50 years have passed. He diagnosed the first case in 1961, a 4-year-old boy who presented with a febrile exanthem. Dr. Kawasaki described the clinical features and proffered the diagnosis in this child as ‘unknown’. This ‘unknown diagnosis’ later became an important step in his serendipitous discovery of a new disease entity that now bears his name. This discovery was based on his deep insight into astute clinical observation and scientific consideration. He reported his cases as a possible new disease at a pediatric meeting at Chiba in 1962, but there was no response. In 1967 at the Tokyo pediatric meeting his presentations met with lot of opposition from his academic peers, who thought what he was describing was nothing other than ‘Still’s disease’ or ‘Stevens–Johnson syndrome’. He had to defend his new observations against many skeptics in the academic community. 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. He collated data on 50 such cases and, in 1967, published an article in the Japanese Journal of Allergy covering 44 pages and with 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 even 50 years after its publication. The first set of guidelines or diagnostic criteria of this disease published in 1970 was mainly based on this article. The cardiac symptoms or findings were not described in this article; two fatal cases had been diagnosed as ‘infantile polyarteritis nodosa’ by the pathologist and so, unfortunately, he excluded these cases from his patient series. In 1970, the first nationwide survey in Japan organized by Drs. Kusakawa, Shigematsu and Kawasaki reported 10 fatal cases and the pathological findings of all autopsy cases demonstrated the same findings as a vasculitis in the medium-sized arteries, particularly with coronary aneurysms, thrombotic occlusion and sudden death.

His first article in the English language described the detailed clinical findings and epidemiology in Japan, and alluded to a small number of patients who had died from myocardial infarction. In 1978 this 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 worldwide, 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, mimicking the complications of adult coronary artery disease (CAD). However, at that time it was not easy to assess the coronary artery lesions associated with KD. Electrocardiography was not helpful for diagnosing coronary aneurysms and 2D echocardiography was not available.

In 1973 I introduced coronary angiography for 20 patients who had recovered from acute KD and 12 of them 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 could exist in children who are asymptomatic. I reported it Dr. Kawasaki soon after and he greatly appreciated our
distinctions in Japan and elsewhere, such as the Takeda Medical Prize (1987), the Medical Award of the Japan Medical Association (1988), the Asahi Prize (1989), the Japan Academy Award (1991), the Japan Pediatric Association Award (2006) and the Special Award for Lifetime Achievement for Contributions to Pediatric Research and Child Health, awarded by the Asian Society for Pediatric Research and Pediatric Academic Societies (2007).

In 1984 he established the Japan Kawasaki disease Research Foundation, which supported nationwide KD surveillance, consultation with patients and parents, and the superb research projects by young investigators, particularly to elucidate the etiology of KD. The Foundation also organized and supported the International Kawasaki Disease Symposium, which started in 1984 and is held in Japan and the USA every 3 years. At the 2018 meeting in Yokohama, 500 participants from 26 countries presented their investigations and engaged in fruitful discussion. The next meeting will be held in Tokyo in 2021, which will uniquely have simultaneous interpretation in English and Japanese to enable better understanding and close discussion.

The study of KD has affected not only pediatric medicine but also several other branches of medicine, such as adult cardiology, rheumatology, vascular pathology, immunology and infectious diseases, and genetics. KD is now the leading cause of acquired heart disease in children in Japan, North America and several other countries. Children with KD are now known to have sequelae that can manifest several years later as coronary events. No adult cardiologist can afford to remain ignorant about the late consequences of KD. The earliest cohorts of patients with KD are now well into adulthood and while the cardiovascular spectrum of KD in childhood is well understood, we are only beginning to understand the long-term implications of such a diagnosis.

In 1989, he was nominated for the prestigious T Duckett Jones Memorial Lectureship by the American Heart Association, which is an honored lectureship for outstanding pediatric cardiologists in the world. I was also invited to attend the meeting and was honored to participate in his lecture. Dr. Kawasaki received a standing ovation after his lecture. Kurume University School of Medicine, our own medical school, invited him to be honorary visiting professor from 1995 and since then he has given lectures for medical students and residents every year. Students revered him as an outstanding teacher and educator.

Dr. Kawasaki received many of the highest honors and distinctions in Japan and elsewhere, such as the Takeda Medical Prize (1987), the Medical Award of the Japan Medical Association (1988), the Asahi Prize (1989), the Japan Academy Award (1991), the Japan Pediatric Association Award (2006) and the Special Award for Lifetime Achievement for Contributions to Pediatric Research and Child Health, awarded by the Asian Society for Pediatric Research and Pediatric Academic Societies (2007).

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Some of the coronary sequelae of KD in these patients seem to merge into adult CAD. A proportion of these patients will need coronary intervention or coronary artery bypass surgery. It is difficult to assess the relative contribution of KD and other risk factors (e.g., aging, obesity, hypertension and smoking) in the development of these coronary lesions. It is also possible that patients with KD may develop premature atherosclerosis. Adult consequences of KD in childhood include acute coronary syndrome, ischemic cardiomyopathy, arrhythmias and valvular heart disease. It is noteworthy that these complications of KD are not seen during childhood. Adult cardiologists need to be aware of the extended spectrum of KD because they will have to deal with these complications.

Another of my concerns is the possible new issue of long-term problems associated with regressed coronary aneurysms. I first described regression of coronary aneurysms in KD, and showed that small or middle-sized aneurysms are likely to regress and demonstrate a normal coronary angiogram within 1 or 2 years after onset, possibly due to positive remodeling, which is a characteristic finding of KD vasculitis. The etiology is probably intimal thickening resulting from proliferation of smooth muscle cells in the media, which makes the arterial lumen appear adequate on angiography. Thus the coronary flow may become relatively normal and as a result, these patients seldom demonstrate significant cardiac events on follow-up to adulthood. However, it is now clear that such patients have abnormal wall structures and endothelial dysfunction, reminiscent of arteriosclerotic lesions. It was recently demonstrated that long-term regressed coronary aneurysms in KD show calcification in the coronary artery wall 30–40 years from the time of their regression, which suggests progression of arteriosclerotic changes continues with aging. Needless to say, the long-term consequences for these patients are entirely uncertain and need further study.

A recent surprise is that some children with the new corona virus infection (COVID-19) demonstrate KD-like symptoms as reported from Europe and the USA. Symptoms such as high fever, skin rash, redness of hands and soles and red swelling of lips are similar to those of KD. COVID-19 is a viral infection, but in KD person-to-person transmission is not evident, and which occurs only in infants and children under 10 years of age. These two diseases may have the same pathophysiological process in part, such as the cytokine storm and activation of endothelial cells and platelets by corona virus, thus demonstrating similar symptoms. This important issue needs to be clarified urgently. In Japan no such patients have been reported so far. Racial and genetic differences may be present. I would very much like to ask Dr. Kawasaki for his opinion on this matter.

Why the incidence of KD has rapidly increased since the time of its first recognition in the 1960s, and continues to increase in Japan, is still unclear. The epidemiologic enigma will perhaps be resolved when we better understand the etiology of this disease. Epidemiology suggests KD may be caused in some susceptible children by a common infectious agent(s) but a direct causal association has not been established. The nationwide surveys in Japan suggest a seasonal peak of incidence in the months of January–March each year for the past 40 years. It is unclear what environmental factors are responsible for this distinct seasonality. It has been hypothesized that a common infectious agent or pathogen-associated molecular pattern may be triggering the cascade. Dr. Kawasaki always said that the etiology and pathogenesis must be identified during his lifetime. That was his dream, and to clarify the mystery of this disease was the strong wish of Dr. Tomisaku Kawasaki.

References


Tribute to Dr. Tomisaku Kawasaki