JACC: CASE REPORTS VOL. 3, NO. 2, 2021
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EDITORIAL COMMENT

Kawasaki Disease in Adulthood*

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Kawasaki disease (KD) is a systemic vasculitis that was first diagnosed in 1961 when Prof. Tomisaku Kawasaki encountered a 4-year-old with unusual symptoms (1). The patient presentation was interpreted as a typical form of scarlet fever or Stevens-Johnson syndrome. In 1962, he saw his second patient with the same constellation of symptoms. Following the collection of 7 cases, he presented his incredible findings at the Japanese Pediatric Society. Five years later, Prof. Kawasaki noticed more than 50 cases with the same presentation; he had labeled it as an acute febrile musculocutaneous lymph node syndrome (2). In 1973, a pathologist discovered the connection to the cardiac disease in 24 children with KD having had coronary artery thrombosis at an autopsy. Subsequently, Prof. Kawasaki spearheaded the KD research committee, which finally published its findings in *Pediatrics* in 1974 (3). For the first time after this publication, it garnered international attention. KD was formally listed in the *Nelson Textbook of Paediatrics*, the standard textbook of pediatrics, in 1992. Prof. Kawasaki subsequently retired but continued to serve as the director of the Japanese KD research center for 2 decades. He had traveled extensively giving lectures and had won several accolades and awards. It is a huge loss for the scientific world, that Prof. Kawasaki passed away on June 5, 2020, leaving an important legacy in congenital heart disease. We are very thankful for him for his incredible work spanning nearly 60 years serving and helping sick children as well as especially helping the medical community recognize and understand a most devastating childhood illness like KD with greater consequences.

As it is well known, the disease is more prevalent in children, with 80% of the cases in the age group between 6 months and 5 years. KD has been diagnosed across all ethnic groups; however, it is 20 times more prevalent in the Asian population. The annual incidence among the Japanese population reached 184 per 100,000 in comparison with the incidence in England hospitals, which is 8 per 100,000 (4,5).

In this issue of *JACC: Case Reports*, Bratincsak et al. (6) show a rare case of an adult presentation of KD. This represents a unique case report due to, first, the age of presentation, as it is quite uncommon to have an adult presentation of KD, and it can be easily misdiagnosed initially. Second, the cardiovascular complications in the form of coronary artery aneurysm (CAA) and subsequent myocardial infarction evolved progressively in the disease course. Third, the diagnosis was established retrospectively by carefully evaluating the patient, who presented with a constellation of signs and symptoms in the context of CAA and myocardial infarction in an adult.

The etiological cause and disease development have been under multiple propositions (7); however, a 2-hit theory of infection and genetic susceptibility has been the most acceptable one. The genetic predisposition in form of polymorphism in IgG receptors in children is believed to increase the susceptibility to the disease and the risk of CAA, and this might explain the ethnic variation in disease incidence (8,9). Given the fact that the disease peaks at a certain time of the year (winter and early spring), infection cause in form of acute bacterial or viral infection has been suspected (10). The presence of the organism in the coronary artery vascular beds was hypothesized to stimulate several growth factor and metalloproteinase, which might have a role in the development of CAA (11).

*Editorials published in the *JACC: Case Reports* reflect the views of the authors and do not necessarily represent the views of *JACC: Case Reports* or the American College of Cardiology.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2021.01.002

The established criteria for the diagnosis by the American Heart Association and the American Academy of Pediatrics is based on the presence of clinical signs and symptoms (12). The disease diagnosed by the history of fever for at least 5 days along with 4 or 5 of the following criteria: bilateral painless nonexudative conjunctivitis; cervical lymphadenopathy, mostly bilateral; maculopapular skin rash; extremity changes in form of acute erythema; and induration of hands and feet followed by desquamation and mucosal changes in form of red cracked lips, glossitis (strawberry tongue), and diffuse erythema of the oral cavity. The disease has been known to be more prevalent in younger age groups, mainly in children around preschool years (4); hence, the adult presentation in this case report is a rare one. The diagnosis of KD is challenging, as most of the time it mimics acute febrile illness, the maculopapular skin rash may be misdiagnosed as a drug reaction to antibiotics administered early in the disease course, and the clinical criteria usually develop sequentially as in this case report, with the patient initially diagnosed with chest cellulites. Moreover, the lack of testing tools in establishing diagnosis makes it challenging in cases in which the patient does not fulfill all the diagnostic clinical criteria.

Inflammatory markers (anemia, leukocytosis, thrombocytosis, and high C-reactive protein and echocardiographic findings [CAA, reduced left ventricular systolic dysfunction, mitral regurgitation, and pericardial effusion]) may help in the diagnosis of a patient who does not have the whole clinical criteria and labeled as incomplete KD (13). In a recent American Heart Association statement, it was reported that echocardiography should be performed when the diagnosis of KD is considered, and repeated at 1 to 2 weeks and 4 to 6 weeks after treatment (12).

CAA is a common complication of KD. The incidence ranges between 30% and 50% in the 9 to 10 days of illness (12). The risk of development of CAA has been attributed to many factors in several studies, including male sex; delay in the initiation of intravenous immunoglobulin (IVIG), as observed in this case report or suboptimal dose; high level of circulating inflammatory biomarkers (C-reactive protein >200 mg/l); and <1 year of age or more than 8 years of age and recurrent KD.

In most cases, the CAA regresses after 10 days; however, about 20% progress (14). The subsequent complications of CAA are of greater concern, including aneurysm thrombosis, myocardial infarction, and deterioration of the left ventricular systolic function, as presented in this case report. Cardiovascular complications are the first cause of death among Kawasaki patients (15). These devastating sequelae can be prevented by establishing a proper diagnosis based on given clinical criteria and early initiation of the optimal dose of IVIG.

The differential diagnosis includes Stevens-Johnson syndrome, scarlet fever, staphylococcal scalded skin syndrome, drug hypersensitivity, toxic shock syndrome, and viral infection.

IVIG and high-dose aspirin are the mainstays of treatment. IVIG 2 g/kg is given as a single infusion over 12 h and may be repeated once in recalcitrant cases. Moderate (30 to 50 mg/kg/day) to high (80 to 100 mg/kg/day) dose of aspirin should be continued until the patient is apyrexial. KD is the only disease for which it is allowed to use aspirin as a treatment line in the children age group; however, it should be combined with the influenza vaccine to guard against Rye syndrome (12). Early initiation of IVIG was found to be protective against the development of CAA (16). Some patients were found to have treatment resistance, and one study suggested a scoring system to predict response to treatment based on the level of circulating inflammatory biomarkers, duration of illness, and age of presentation (17). The use of corticosteroids did not show marked beneficial effects in comparison with placebo in the context of cardiovascular complications (18).

The KD patient cohort is currently growing and represents a challenge in terms of increased cardiovascular disease risk stratification. The worst prognosis is among patients with giant aneurysms (>8 mm); however, the risk of subsequent myocardial infarction in patients with small aneurysms is uncertain. The state of vascular inflammation and endothelial injury impacts coronary flow reserve and makes those patients more vulnerable to accelerated atherosclerosis. Ongoing registry studies and prospective data are aiming to provide optimal management of Kawasaki patients with CAA with regard to the thrombotic regimen (antiplatelets vs. anticoagulation or combined regimen). These conundrums in clinical management are of paramount importance and warrant future prospective studies for a better understanding of disease progression.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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JACC: CASE REPORTS, VOL. 3, NO. 2, 2021
FEBRUARY 2021:280–2

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KEY WORDS myocardial infarction, myocardial ischemia, thrombosis