Myocarditis in Kawasaki Syndrome
A Minor Villain?
Masato Takahashi, MD

Twenty-two years have passed since the original description by Tomisaku Kawasaki of the syndrome that now bears his name. The syndrome is now known to occur throughout the world. The true annual incidence in the United States is unknown, but overall incidence is estimated to be 4.5–9.5 per 100,000 children under 5 years of age in nonepidemic years, whereas during epidemics, the incidence increases several fold. In contrast, the incidence of acute rheumatic fever has been as low as 1 per 100,000 inhabitants of all ages; however, geographic pockets have reported sporadically higher incidences in recent years. The incidence of viral myocarditis is difficult to assess. As of 1989, Kawasaki syndrome appears to be one of the leading causes of acquired heart disease in children.

Despite an intensive international search, the etiologic agent of Kawasaki syndrome has eluded researchers. Various biologic and nonbiologic agents have been proposed and then discarded one by one for lack of independent confirmation.

Coronary artery complications have been considered a major villain in Kawasaki syndrome. Deaths have been almost exclusively the result of myocardial infarction. However, the mortality rate has fallen from 2% in 1971 to a current level of 0.3%. This decline in mortality has been brought about by a series of developments. First, echocardiography has become established as a reliable detection tool, enabling us to identify coronary artery aneurysms with a high degree of accuracy. Second, treatment with antiplatelet drugs, primarily aspirin, has been generally credited with preventing myocardial infarction. Third, Furusho and coworkers have pioneered intravenous gamma globulin therapy, which has been effective in reducing the frequency of coronary artery abnormalities. A US multicenter study subsequently confirmed the efficacy of gamma globulin not only in reducing coronary artery abnormalities but also in shortening the duration of systemic inflammation. Rowley et al, in a retrospective study, showed that intravenous gamma globulin may prevent formation of giant coronary artery aneurysms, which were shown previously to be associated with a significantly worse prognosis for coronary artery occlusion. In a small number of patients who developed coronary thrombosis, intravenous thrombolytic therapy has been performed with at least short-term successes. Aortocoronary bypass surgery holds increasing hope for patients at risk for life-threatening myocardial infarction through the works by Kitamura and others in Japan. Thus, we are gradually gaining mastery over our major villain: the coronary artery disease of Kawasaki syndrome.

What about myocarditis of Kawasaki syndrome? Clinical, electrocardiographic, or echocardiographic signs of myocarditis are recognizable in the first 3 weeks of illness in over 50% of patients. We and others have observed positive cardiac uptake of gallium 67 in 60–80% of patients with Kawasaki syndrome. Positive gallium uptake by the myocardium is generally believed to be mediated by infiltrating leukocytes.

Cellular infiltration and edema in the myocardium are often found in postmortem examination of patients who died within 30 days from onset of Kawasaki syndrome. More alarming is the finding of Yutani and associates that myocardial biopsies performed in 201 patients from 1 month to 11 years after the onset of disease all showed varying degrees of cellular infiltration, fibrosis, and abnormal myocyte structure. These findings need further reinterpretation and confirmation with more standardized histopathologic criteria for myocarditis and with electron microscopic and immunofluorescent histochmical techniques.

In most patients, however, the degree of myocarditis is so mild that anticoagulative therapy is not required. Rare patients develop profound cardiac failure. Thus, in the acute clinical setting, myocarditis appears to be a minor villain.

The mechanism of myocarditis in Kawasaki syndrome is unknown. However, mediation by the immune system is likely. Leung and others showed in vitro that activated macrophages perhaps reacting to an unknown etiologic agent produce cytokines that uncover new antigens in the vascular...
endothelium, which in turn are lysed by immunoglobulin M antibodies contained in the patients’ acute sera.\textsuperscript{15} Although this mechanism may be responsible for coronary and peripheral arteritis, a similar autoimmune mechanism may be at work against structures within the myocardium. If that were true, one could speculate a commonality of mechanism between Kawasaki myocarditis and viral (such as coxsackievirus) myocarditis. A series of animal models of coxsackievirus myocarditis\textsuperscript{16,17} suggest cell-mediated and humoral immune mechanisms at work against myocytes.

Newburger and others\textsuperscript{18} in this issue of Circulation showed that velocity of circumferential fiber shortening corrected for wall stress, an echocardiographic load-independent index of left ventricular performance, was reduced in patients with Kawasaki syndrome during and after the acute illness up to 3 months and improved spontaneously by 1 year after the illness.\textsuperscript{18} Functional reversibility of Kawasaki myocarditis suggests that the target of such autoimmune attack is a relatively renewable structure such as intramyocardial microvessels rather than more highly specialized and nonrenewable structures such as myofilaments and mitochondria. Alternatively, if the target organelles were the same as in viral myocarditis, the intensity or duration of attack may be so limited that only minor damage is inflicted. The fact that patients with Kawasaki syndrome endure severe systemic inflammation for 2 or more consecutive weeks without permanent and measurable myocardial dysfunction favors the former scenario. The pathogenetic mechanism and target structures in myocarditis are fascinating subjects for further research. According to Newburger et al.,\textsuperscript{18} the presence of left ventricular dysfunction appears unrelated to the presence or absence of coronary artery abnormalities. The fact that coronary artery abnormalities in Kawasaki syndrome show more individual variability and nonuniformity than myocarditis may be ascribed to factors other than histopathologic processes, such as unevenly applied mechanical stresses of constant bending and stretching imposed by cardiac motion and acute rises in intraluminal pressures of major coronary arteries during systole when there is no runoff into the intramural perforating branches.

Newburger and associates,\textsuperscript{18} furthermore, showed that in those patients who were treated with intravenous gamma globulin and aspirin the left ventricular performance seemed to improve more rapidly compared with left ventricular performance in patients who were treated with aspirin alone. Although the mode of action of gamma globulin in this disease is not yet clearly defined, its demonstrated beneficial effect on myocarditis lends further support to immune-mediated mechanisms of myocarditis.

The specter of chronic persistent subclinical myocardial changes raised by Yutani and coworkers\textsuperscript{13} gives us pause. If chronic cardiomyopathy indeed follows acute Kawasaki syndrome, such ongoing insult throughout childhood could conceivably lower the threshold for ultimate cardiac decompensation due to any one of the cardiac diseases that occur with adulthood. It may be a minor villain at first but could emerge as an accomplice in a major drama in later life. If intravenous gamma globulin does hasten recovery of left ventricular function, the patient may sustain a lesser degree of permanent histologic changes, which could translate into greater functional reserve. Born with only one heart, a child with Kawasaki syndrome would be pleased to learn that the therapy that relieves the fever and protects the coronary arteries during the acute illness also gives him a shortened period of acute myocarditis.

References

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