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REVIEW TOPIC OF THE WEEK

Kawasaki Disease

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ABSTRACT

Kawasaki disease is an acute, self-limited vasculitis of unknown etiology that occurs predominantly in infants and children. If not treated early with high-dose intravenous immunoglobulin, 1 in 5 children develop coronary artery aneurysms; this risk is reduced 5-fold if intravenous immunoglobulin is administered within 10 days of fever onset. Coronary artery aneurysms evolve dynamically over time, usually reaching a peak dimension by 6 weeks after illness onset. Almost all the morbidity and mortality occur in patients with giant aneurysms. Risk of myocardial infarction from coronary artery thrombosis is greatest in the first 2 years after illness onset. However, stenosis and occlusion progress over years. Indeed, Kawasaki disease is no longer a rare cause of acute coronary syndrome presenting in young adults. Both coronary artery bypass surgery and percutaneous intervention have been used to treat Kawasaki disease patients who develop myocardial ischemia as a consequence of coronary artery aneurysms and stenosis.
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Kawasaki disease (KD) is an acute, self-limited vasculitis of unknown etiology that occurs predominantly in infants and young children. Manifested initially by high fever, mucocutaneous inflammation, and cervical lymphadenopathy, KD targets the coronary arteries and other cardiovascular structures (1). Approximately 1 in 5 children who are not treated with intravenous immunoglobulin (IVIG) in the acute phase of illness develop coronary artery aneurysms (CAA). Indeed, KD has replaced rheumatic fever as the leading cause of acquired cardiac disease in children in the developed world. This review describes our current understanding, as well as knowledge gaps, of the pathophysiology of KD and general principles guiding the care and management of these patients in the absence of evidence-based guidelines (**Central Illustration**). Diagnostic criteria for complete and incomplete KD are detailed in the 2004 American Heart Association/American Academy of Pediatrics guidelines (2).

EPIDEMIOLOGY

The epidemiology of KD may yield important clues to the etiology of this mysterious disease. First, KD strikes predominantly infants and young children; 80% of patients are younger than 5 years of age, although the disease can occur even in adolescence. The young age of onset suggests that susceptibility may be linked to maturation of the immune system. Second, although KD has been recognized on every continent and in all racial groups (3), the incidence of disease varies widely among different populations. In Japan, the country of highest incidence, the numbers of cases are steadily increasing and the most recent survey reported an incidence of 265 cases per 100,000 children <5 years of age (4). In the United States, passive surveillance and analysis of administrative databases suggest a national incidence in children <5 years of age of 19 per 100,000, with a higher rate of 24.7 per 100,000 reported for California (5). An important genetic contribution to disease

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susceptibility is suggested by the higher incidence among U.S. children of Asian/Pacific Islander descent in Hawaii and California (210 and 50.4 per 100,000, respectively) (6,7). A distinct seasonality is coherent across the Northern Hemisphere (8).

The current KD paradigm is that an immunologic reaction is elicited in genetically susceptible hosts upon exposure to the KD trigger(s), thought to be widely dispersed in the environment and to enter through the upper respiratory tract (9). A subset of genetically susceptible children (~25%) will suffer irreversible damage to the coronary arterial wall. There is no evidence to support person-to-person spread, although temporal and spatial clustering of cases is well-documented (10). Two potential paradigms postulate that the trigger is either of the following: 1) an infectious agent that replicates in the superficial epithelial cells of the upper airway (11); or 2) an antigen widely dispersed in the environment. Recent intriguing data support the hypothesis that the trigger for KD is carried by large-scale tropospheric winds and that provinces in northeastern China serve as a source region for the seasonal clustering and annual epidemic of KD cases in Japan, Hawaii, and southern California (12).

PATHOPHYSIOLOGY

The complex picture that is emerging of the immune response in acute KD includes activation of both the innate and adaptive immune systems. Neutrophils are among the first responders to invade the arterial wall and are followed by $CD8^+$ T cells, dendritic cells, and monocyte/macrophages (13,14). Strong support for activation of the interleukin (IL)-1 pathway includes increased transcript abundance for IL-1-related genes by microarray and quantitative real-time polymerase chain reaction, and by increased levels of IL-1 pathway proteins in plasma from acute KD patients (15). In KD, as in giant cell arteritis (16), 2 dominant cytokine clusters are recognized: the IL-6/T helper (Th)-17 axis and the IL-12/interferon gamma axis. IL-6, in combination with transforming growth factor beta (TGFβ), polarizes naïve T cells toward a Th-17 phenotype, resulting in these cells invading the vessel wall and elaborating a proinflammatory cytokine profile (17,18). Evidence is accumulating that, in a subset of patients who develop CAA, the IL-12/interferon gamma axis may be activated and proinflammatory cytokines may play a role in inducing activation of Th-1 cells in the vessel wall (19–22).

Mouse models of coronary arteritis mimicking KD have been created by intraperitoneal injection of cell wall extracts of both *Lactobacillus casei* and *Candida albicans* into certain genetic strains (23). These models have been used to interrogate responses to different therapies and provide support for the use of IVIG, blockade of tumor necrosis factor alpha and IL-1, and, potentially, the use of atorvastatin to modulate the acute phase of vascular wall inflammation (24–26).

The complex genetics of KD is beginning to yield to efforts by multinational collaborative groups to determine the genetic influences on disease susceptibility and outcome (27). Roughly 65% of the genetic risk for KD susceptibility is accounted for by polymorphisms in calcium signaling pathways, the TGFβ pathway, and human leukocyte antigens (28–31).

PATHOLOGY

The pathological changes in KD affect medium-sized, extra-parenchymal muscular arteries, most commonly the coronary arteries. A recent comprehensive review of 32 KD autopsies and 8 explanted hearts described 3 linked vasculopathic processes in the arterial wall: necrotizing arteritis, subacute/chronic vasculitis, and luminal myofibroblastic proliferation (LMP) (32). The acute arteritis is characterized by a neutrophilic infiltrate originating from the lumen of the vessel and can be associated with extensive necrosis of all layers of the vessel wall in both the coronaries and other medium-size arteries (13). Neutrophil elastases may also play a role in destruction of the internal and external elastic laminae that provide recoil for the vessel wall and whose destruction contributes to aneurysm formation. Neutrophil elastase inhibitors have been used in Japan to block this pathway, but no randomized clinical trial data are available (33).

Subacute vasculitis begins weeks after the onset of fever, can still be detected months to years later, and is closely associated with the third process, LMP (32). The inflammatory infiltrate is predominantly lymphocytic and originates in the adventitia. $CD8^+$ cytotoxic T lymphocytes have been documented in the media (14), suggesting that anti-T-cell therapies, such as the calcineurin inhibitors cyclosporine and tacrolimus, might be effective (34,35). LMP, with myofibroblasts possibly derived from medial smooth muscle cells, is a pathological process that is likely mediated by TGFβ (36,37). Polymorphisms in the TGFβ pathway are associated with increased susceptibility to aneurysm formation in KD patients (30). LMP can

ABBREVIATIONS AND ACRONYMS

CAA = coronary artery aneurysm

CABG = coronary artery bypass graft

CMR = cardiac magnetic resonance

CTA = computer tomographic angiography

IL = interleukin

IVIG = intravenous immunoglobulin

KD = Kawasaki disease

LMP = luminal myofibroblastic proliferation

MI = myocardial infarction

PCI = percutaneous coronary intervention

TGFβ = transforming growth factor beta

Th = T helper