JACC: ADVANCES VOL. 3, NO. 6, 2024

EDITORIAL COMMENT

Shining a Light

Ocular Coherence Tomography and the Pathology of Late Convalescent Kawasaki Disease*

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Kawasaki disease (KD) is an acute self-limited vasculitis of childhood characterized by high fever, mucocutaneous inflammation, and unilateral cervical lymphadenopathy.[1] This syndrome occurs in all racial groups, but children of Japanese ancestry have the highest relative risk. Indeed, by age 10 years, 1 in every 65 boys and 1 in every 82 girls in Japan have been diagnosed with KD.[2] The acute signs and symptoms of KD are transient, leaving coronary artery aneurysms (CAA) as its most serious long-term complication. Using American Heart Association *z*-score criteria, with adjustment of coronary diameter for body surface area, coronary abnormalities occur in ~25% of affected children and ~50% of infants age <6 months. Timely treatment with high-dose intravenous immunoglobulin can markedly reduce the risk of CAA formation. Almost all cardiovascular morbidity and mortality occurs in the 1% of KD patients who develop large or giant CAA, defined by *z*-score ≥10 or maximum absolute dimension of ≥8 mm. These patients are at the highest risk for developing ischemic heart disease, including angina, acute myocardial infarction, and progressive coronary stenosis. Smaller aneurysms most often remodel to decreased or normal lumen diameter and have a better prognosis.

Long-term management of KD patients is informed by the patient's worst-ever and current coronary artery *z*-scores because coronary physiology and histopathology are abnormal in both current and regressed CAA.[1] Postmortem studies have shown that KD vasculopathy is a necrotizing arteritis, with segmental destruction and weakening of the arterial wall and formation of aneurysms beginning in the first 2 weeks of illness.[3] Acute neutrophilic infiltration gives way to chronic inflammation that can smolder for months or even longer.[4] Luminal myofibroblastic proliferation may reduce lumen dimension but also causes progressive coronary stenosis. Calcification occurs predominantly within organized thrombus and occasionally within the intima, increasing with time from illness onset and greatest in aneurysms of larger diameter.[5] Autopsy studies have been conflicting in their assessment of whether atherosclerosis occurs in KD vasculopathy.[3,4] Mortality in KD is fortunately rare, and postmortem series are small and biased toward the worst cases, creating a need for in vivo studies of coronary architecture and physiology.

In the current issue, Shiono and colleagues report their findings in a single-center series using optical coherence tomography (OCT) in 61 coronary arterial segments in 24 patients, a median of 16.6 years after KD onset (median age at OCT = 18.4 years).[6] All patients in the acute phase, with a median age at illness onset of 1.2 years, had had a coronary aneurysm in at least one major coronary artery. Two patients had had a myocardial infarction; one subsequently had surgical revascularization. Findings on OCT were compared among 17 segments with persistent CAA, 29 with regressed/remodeled CAA, and 15 segments that did not have CAA by initial angiography. Although atherosclerosis was most prominent in segments with persistent aneurysms, the arterial wall was abnormal in all coronary arterial segments examined by OCT. Calcification, microvessels, cholesterol crystals,

*Editorials published in *JACC: Advances* reflect the views of the authors and do not necessarily represent the views of *JACC: Advances* 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 2772-963X https://doi.org/10.1016/j.jacadv.2024.100938

macrophage accumulation, and layered plaque were most common in persistent aneurysmal segments and least common in those segments without early aneurysms; regressed segments had abnormalities of intermediate severity. Importantly, even segments without known aneurysmal involvement showed intimal thickening, medial disruption, presence of microvessels, and macrophage accumulation, although cholesterol crystals and layered plaque were not present. Layered plaque was a frequent finding in both regressed and persistent aneurysms, suggesting subclinical thrombosis in these vessels.

OCT offers axial resolution an order of magnitude greater than that of intravascular ultrasound, and its ability to define features of the vessel wall has been well-validated.[7] OCT was first deployed to evaluate the in vivo pathology of KD a decade ago.[8] Since then, fewer than a 100 KD patients have been studied with this modality. Previous work has demonstrated a high prevalence of intimal thickening in coronary segments affected by CAA in children and young adults at late follow-up, often associated with medial thinning/disruption.[9] These abnormalities are most pronounced in coronaries with persistent aneurysms, but may also be seen in segments with normalized angiographic appearance. Two published studies evaluating grossly unaffected coronary branches in KD patients with at least one CAA have presented conflicting findings as to whether the never-aneurysmal segments also display intimal thickening.[10,11] The current report would seem to "break the tie," suggesting that even seemingly normal segments display chronically abnormal laminar anatomy and that resolution of aneurysms on echocardiogram/angiography does not herald a normalization of vascular biology.

Shiono et al also extend and enrich our understanding of the qualitative abnormalities that may be seen in KD coronaries. Previous studies have observed fibrosis, macrophage infiltration, and microvessels in segments with and without a history of CAA. Calcification has been largely confined to segments with persistent aneurysms, including those that have progressed to stenosis and clinical ischemia.[10,12,13] The current series is the first to report the finding of layered plaques in KD, here found exclusively in coronary segments with persistent or regressed CAA. In the setting of atherosclerotic coronary artery disease, this histology indicates plaques that have ruptured and healed without causing coronary occlusion.[12] Whether the pathophysiology of layered plaques in KD represents the same process or reflects remote immune disruption of the vessel wall with subsequent thrombosis and healing remains an open question.

This study has several limitations. Findings in a small series of severe KD cases who had at least one CAA may not be generalizable to most KD patients, and especially to those who never had a CAA in any artery at any time of illness. For example, arterial segments that were classified as normal in this series based on their appearance on initial coronary angiography might have had earlier coronary artery dilation that had already regressed. No information is presented on the variation of findings across the length of studied coronary segments. The study could not correlate OCT findings with risk factors for atherosclerotic coronary artery disease, including lipid levels, blood pressure, and family history. The age of patients at OCT was both young and tightly clustered. Finally, the predictive validity of OCT findings for later vascular health could not be ascertained with a cross-sectional study design. Longitudinal follow-up of this cohort using invasive or noninvasive assessment of coronary architecture and function would be invaluable.

In summary, clinical and epidemiologic studies have not yet established whether KD accelerates atherosclerosis, in part because many of those followed systematically since establishment of serial Japanese nationwide surveys are still younger than age 40 years.[13] It is projected that, by 2030, one in every 1,600 adults in the United States will have had KD in childhood,[14] and even now, a series suggests that ~5% of adults younger than age 40 years who undergo coronary angiography for suspected myocardial ischemia have coronary sequelae of KD.[15] Thus, it is timely and important for future research to explore methods to assess late atherosclerotic coronary artery disease in KD survivors who have had a spectrum of coronary involvement. Until then, the findings of Shiono et al reinforce the importance of preventive cardiology counseling, risk factor management including consideration of statin therapy, and thromboprophylaxis for KD patients in accordance with 2017 American Heart Association recommendations.[1]

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The McCance Family Foundation (JWN) is a funding source for this paper. Dr Newburger has received royalties from UpToDate. Dr Esch has reported that he has no relationships relevant to the contents of this paper to disclose.

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KEY WORDS coronary artery disease, Kawasaki disease, pediatric cardiology, vasculitis