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Authors

Gordon, John B
Daniels, Lori B
Kahn, Andrew M
et al.

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The Spectrum of Cardiovascular Lesions Requiring Intervention in Adults After Kawasaki Disease

John B. Gordon, MD,[a] Lori B. Daniels, MD,[b] Andrew M. Kahn, MD,[b] Susan Jimenez-Fernandez, MD,[c] Matthew Vejar, BS,[c] Fujito Numano, MD,[c] Jane C. Burns, MD[c]

ABSTRACT

OBJECTIVES The aim of this study was to characterize the range of management issues raised by adults with cardiovascular sequelae from Kawasaki disease (KD) in childhood.

BACKGROUND Aneurysms resulting from vascular inflammation associated with KD in childhood may remain clinically silent until adulthood. Adults with large aneurysms, unstable angina, or myocardial infarction following KD in childhood present unique challenges to interventional cardiologists and cardiothoracic surgeons.

METHODS In an observational study of adults with histories of KD in childhood, data were collected regarding the medical histories and outcomes of 154 adult KD patients, of whom 21 underwent either percutaneous interventions or surgery.

RESULTS Of the 21 subjects with interventions, 11 had been diagnosed with KD in childhood, and 10 had histories of KD-compatible illnesses. Seventeen subjects were asymptomatic until experiencing acute cardiovascular symptoms: acute myocardial infarction (n = 12), angina (n = 2), end-stage congestive heart failure requiring cardiac transplantation (n = 1), and claudication (n = 2).

CONCLUSIONS Cardiovascular complications in these subjects illustrate the following points: 1) even small to moderate-sized aneurysms that "normalize" on echocardiography in childhood can lead to stenosis and thrombosis decades after the acute illness; 2) coronary interventions without intravascular ultrasound may result in clinically significant underestimation of vessel luminal diameter; 3) failure to assess the extent of calcification may lead to suboptimal procedural outcomes; and 4) patients with symptomatic peripheral aneurysms may benefit from endarterectomy or resection. Interventional cardiologists should be aware of the potential challenges in treating this growing population of adults. (J Am Coll Cardiol Intv 2016;9:687–96) © 2016 by the American College of Cardiology Foundation.

Information on the extent of cardiovascular disease in adults following Kawasaki disease (KD) in childhood is only now emerging, despite the fact that Tomisaku Kawasaki described his first pediatric patients more than 45 years ago (1). System dynamic models suggest that by 2030, 1 in every 1,600 adults in the United States will have had KD (2). Despite the efficacy of high-dose intravenous immunoglobulin in preventing coronary artery damage, approximately 5% to 7% of treated patients will develop coronary artery pathology with the attendant risk for thrombosis or stenosis later in life (3,4). With current U.S. Census Bureau projections of a U.S. population of 360 million by 2030 and 78% of the

population 18 years and older, there will be 175,000 adult KD patients, of whom 12,000 will have coronary aneurysms (5).

Autopsy and cardiac catheterization studies have established that the diagnosis of KD may be missed in childhood, and important cardiovascular damage may remain silent until adulthood, when thrombosis or critical coronary artery stenosis results in an acute ischemic event (6,7). Because the etiology of KD remains unknown, there is no specific diagnostic test, the acute illness is self-limited, and the physical signs and laboratory findings mimic other childhood illnesses, pediatric patients will continue to be misdiagnosed. This has created a population of young adults with significant cardiovascular damage who are unaware of their antecedent KD and risk for acute coronary syndromes or myocardial infarction (MI). No systematically collected data are available to inform physicians on the natural history of KD decades after the initial illness in childhood.

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To address this issue, the San Diego Adult KD Collaborative study was initiated as a longitudinal, observational study of young adults with childhood histories of KD. The present series focuses on the lessons learned from the subset of subjects who experienced challenging cardiovascular sequelae that required either catheter-based or surgical interventions.

METHODS

As of July 1, 2014, the San Diego Adult KD Collaborative study had enrolled 154 young adults (>15 years of age) in a longitudinal study of the cardiovascular sequelae of KD. A subset of patients who lived locally or were able to travel to San Diego underwent cardiac imaging with computed tomographic calcium scores. Computed tomographic angiography was performed on the subset of subjects with clinical indications such as a history of cardiovascular abnormalities or a positive calcium score. Of the 154 subjects, 63 (40.9%) were originally diagnosed with KD in childhood and followed by 1 of the coauthors (J.C.B.) and were designated as cohort 1. This group of unselected subjects followed since disease onset can inform us about the natural history of KD. These 63 subjects had been followed for a mean of 18.0 years (range: 6.7 to 30.1 years), and 8 had aneurysms. The remaining 91 subjects (cohort 2), of whom 30 had aneurysms, were diagnosed with KD elsewhere and were referred by their

physicians or self-referred for participation in the study. Thus, cohort 2 was likely biased toward subjects with more severe outcomes who might be more likely to seek participation in a study. Overall, 21 subjects (1 from cohort 1 and 20 from cohort 2) had undergone percutaneous interventional or surgical cardiovascular procedures and are included in this report. The demographic and clinical features of the study population are summarized in **Table 1**. The study was approved by the Institutional Review Board at the University of California, San Diego. All parents gave written informed consent for the participation of subjects younger than 18 years, and subjects gave written assent or consent as appropriate.

RESULTS

Of the 21 subjects who underwent interventions, 11 were diagnosed with KD in childhood, while 10 were retrospectively determined to have had KD (**Figure 1**). Of the 11 patients who were diagnosed in childhood, 9 were recognized to have coronary artery aneurysms at the time of their initial illness, and 2 (#13 and #20) were thought to have only coronary artery dilation that resolved. Eight of the 11 subjects diagnosed in childhood with aneurysms were followed by cardiologists, and only 1 (#1) had an acute cardiovascular event that was treated with an emergent intervention. Three of 11 subjects were not followed longitudinally, and 1 (#20) required emergent percutaneous coronary intervention (PCI) with stenting, 1 (#13) required emergent bypass surgery for critical stenosis in the left main coronary artery, and 1 (#11) ultimately required cardiac transplantation for ischemic congestive heart failure. Of the 10 subjects without diagnoses of KD in childhood, presumed diagnoses of KD were made at the time of their acute presentation with either angina (n = 1) or acute MI (n = 9).

PCIs. Eight subjects presented with acute cardiac symptoms and underwent emergent percutaneous transluminal coronary angioplasty (PTCA) (**Table 2**). Of these 8 subjects, 6 did not have diagnoses of KD in childhood, while 2 subjects (#11 and #20) had been diagnosed with KD but subsequently released from care. Antegrade flow was established by PTCA in 6 of the 8 subjects (**Figure 2**). In 1 subject (#14), organized thrombus of the right coronary artery (RCA) prevented passage of the angioplasty catheter. In another subject (#11), passage of the angioplasty catheter through a tight stenosis in the left anterior descending coronary artery (LAD) led to cardiac arrest. Heavy calcification in the arterial wall precluded angioplasty of the vessel, and the subject ultimately

underwent cardiac transplantation for irreversible ischemic cardiomyopathy.

COMPLICATIONS OF PTCA. Two subjects had complications of PTCA. Patient #17, a 38-year-old Vietnamese man, presented with an acute MI with no known history of KD or other cardiovascular disease. At cardiac catheterization, occlusion of the proximal RCA was treated with PCI using a 3.0-mm drug-eluting stent that was post-dilated to 3.5 mm. There was restoration of Thrombolysis In Myocardial Infarction flow grade 2. Medical management included aspirin and clopidogrel, and the diagnosis of KD was not suspected at this time. The subject returned 2 weeks later with unstable angina. Repeat angiography and intravascular ultrasound (IVUS) demonstrated resolution of the acute thrombus but also revealed a 5.5-mm aneurysm that had not been previously appreciated; thus, the diagnosis of missed KD in childhood was suspected (Figure 3). The undersized stent was post-dilated but remained malopposed because of stent-vessel mismatch. Medical management included warfarin, aspirin, clopidogrel, and simvastatin. Interview of the subject's parents revealed a KD-compatible illness at the age of 6 years.

Patient #15, a 33-year-old Laotian man, presented with an ST-segment elevation MI with no history of cardiovascular disease. At cardiac catheterization, he was found to have a completely occluded RCA. The RCA aneurysm measured 10 mm at it widest point. It began at the ostium and extended to the bifurcation of the posterior descending and posterolateral branches. There was an 8-mm aneurysm of the LAD, and a long, ectatic segment of the left circumflex coronary artery measuring 4 mm. Although he was not known to have had KD in childhood, a history of a KD-compatible illness at age 5 years was elicited from his family. The acute RCA occlusion resolved with PTCA and antithrombotic plus antiplatelet therapy (aspirin, heparin, eptifibatide, clopidogrel, and warfarin). No significant obstruction in the RCA was present. Reocclusion of the RCA aneurysm occurred 3 years later despite aspirin and warfarin therapy, with good patient compliance and an international normalized ratio in the target range (2.0 to 3.0). The reoccluded RCA could not be successfully reopened percutaneously. The subject now has chronic, stable angina that is managed medically with aspirin, metoprolol, and isosorbide mononitrate.
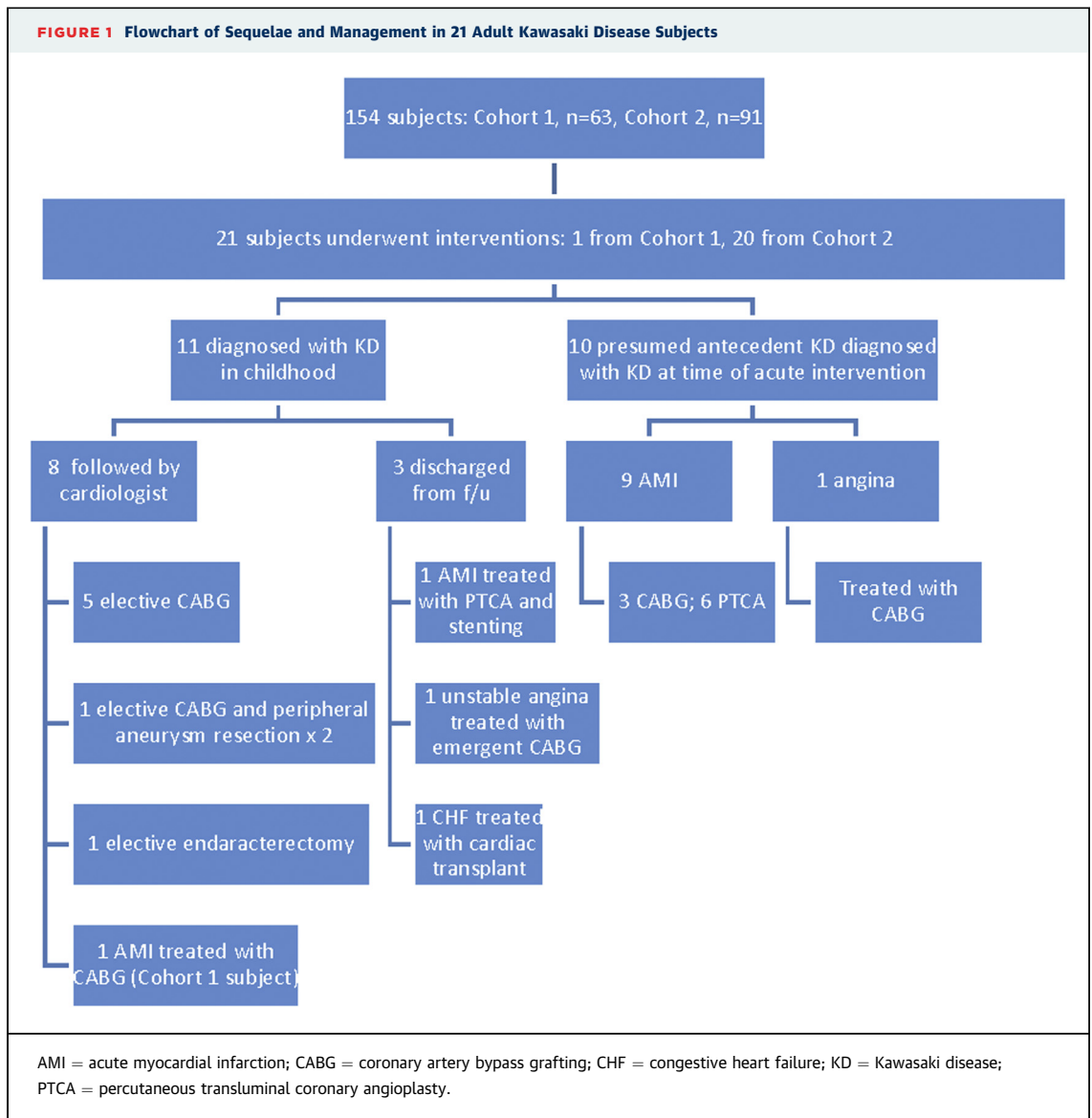
CORONARY ARTERY BYPASS GRAFTING. Twelve subjects underwent coronary artery bypass grafting (CABG) (5 subjects with internal mammary artery grafts, 3 subjects with saphenous vein grafts, and

TABLE 1 Demographic and Clinical Characteristics of the Study Population in Order of Age at Intervention

Patient #	Age at KD Onset (yrs)	Sex	Ethnicity	Age at Enrollment (yrs)	Age at Intervention (yrs)	CV Risk Factors at Enrollment
1	1.5	Male	Hispanic	15	4	None
2	5	Female	White	33	11	Previous smoker
3	14	Male	Chinese	15	14	None
4	6	Female	White	15	16	None
5	1.5	Female	White	16	17	None
6	5	Female	White	41	18	None
7	0.25	Female	White	21	19	None
8	17*	Male	Vietnamese	26	22	Mixed hyperlipidemia
9	2	Male	Caucasian	28	23	None
10	13*	Female	African American	44	24	None
11	3	Male	White	30	29	None
12	0.125	Male	White	30	30	None
13	4	Male	White	33	32	Mixed hyperlipidemia
14	6*	Male	White	58	32	Mixed hyperlipidemia, hypertension
15	5*	Male	Laotian	38	33	Mixed hyperlipidemia, previous smoker
16	7*	Male	Singaporean	59	33	Type 2 diabetes, hypertension, mixed hyperlipidemia
17	6*	Male	Vietnamese	38	38	Mixed hyperlipidemia, smoker
18	5*	Male	Caucasian	47	44	Mixed hyperlipidemia
19	2*	Male	Japanese		49	None
20	12	Male	White	51	49	None
21	8*	Male	Filipino	57	53	Mixed hyperlipidemia

*KD-compatible illness in childhood not diagnosed as KD.

CV = cardiovascular; KD = Kawasaki disease.

4 subjects with combination grafting), with variable results. Six subjects underwent elective CABG, and 6 had emergent procedures. Surgical intervention was chosen for a variety of different reasons in these subjects. Patient #4 was diagnosed with KD complicated by giant aneurysms at 6 years of age and was maintained on aspirin and warfarin, with good compliance. She had a stable 15-mm RCA aneurysm and a progressively enlarging LAD aneurysm that measured 7 mm at the time of initial KD diagnosis and 25 mm at the time of surgery 11 years later (Figures 4A and 4B). Because of concern for potential aneurysm rupture, the subject underwent modification of the LAD aneurysm with elective CABG. A left internal mammary artery graft was placed to the distal LAD and a saphenous vein graft to the distal RCA. A pericardial patch directed flow from the left main coronary artery into the circumflex coronary artery. The wall of the resected aneurysm showed replacement of the normal vessel architecture with hyaline degeneration (Figure 4C). Another subject (Patient #5) underwent elective CABG because of progression of

FIGURE 1   Flowchart of Sequelae and Management in 21 Adult Kawasaki Disease Subjects

AMI = acute myocardial infarction; CABG = coronary artery bypass grafting; CHF = congestive heart failure; KD = Kawasaki disease; PTCA = percutaneous transluminal coronary angioplasty.

stenosis at the outlet of a heavily calcified 8-mm LAD aneurysm, an abnormal fractional flow reserve (0.74), and the patient's desire to discontinue warfarin therapy. She was asymptomatic and had normal results on stress echocardiography. Surgery was performed with a left internal mammary artery graft to the distal LAD and a right internal mammary artery graft to the circumflex artery. The subject continues to be asymptomatic 18 months following her surgery.

In two young female subjects ages 18 and 24 years (#6 and #10), the diagnosis of MI was delayed because of a failure to attribute their severe chest pain to myocardial ischemia. However, once the ischemia was recognized, both subjects underwent coronary angiography followed by CABG with venous grafts

that are still functional 28 and 30 years later, respectively.

One subject (#13) had "dilation of the coronary artery" with his acute KD at age 4 years that resolved on echocardiography, and he was released from care. Details of the location and nature of the dilation were not available. At the age of 32 years, he developed unstable angina due to severe stenosis of the left main coronary artery that was treated emergently with CABG, with good results. This subject subsequently had a calcium volume score of 666 mm³, performed as part of our study that, in retrospect, could have alerted physicians to the presence of significant coronary artery damage had the score been obtained as a screening procedure earlier in life (8,9).

TABLE 2 Cardiovascular Status, Complications, and Interventions in 21 Adults With Known or Suspected Histories of Kawasaki Disease in Childhood

Patient #	CV Status Prior to Intervention	CT Calcium Score (mm³)	CV Manifestations	Intervention for Complication
1	8.4-mm RCA aneurysm; 4.1-mm LMCA aneurysm, 4.6-mm LAD aneurysm	667	4 yrs: STEMI with thrombotic occlusion of proximal RCA aneurysm	CABG: RIMA to distal RCA, implanted proximal to distal RCA aneurysm
2	7.4-mm proximal and 5.1-mm distal RCA aneurysms, 4.8-mm Cx aneurysm	2,123	11 yrs: abnormal stress test results	CABG: LIMA to LAD
3	10-mm LAD aneurysm, 8-mm Cx aneurysm, 16-mm RCA aneurysm	ND	15 yrs: asymptomatic with occluded LAD and RCA by CT angiography	CABG: LIMA and RIMA to distal LAD and to RCA
4	9-mm progressing to 25-mm LAD aneurysm; 15-mm RCA aneurysm	396; ring calcification noted on CXR	17 yrs: asymptomatic with progressively enlarging LAD aneurysm	CABG: LIMA to LAD, reconstruction of LMCA to Cx with pericardial patch, RIMA to RCA with insufficient flow followed by reverse SVG from aorta to distal RCA
5	9-mm LAD aneurysm	ND; ring calcification noted on CXR	16 yrs: FFR 0.74 at outlet of LAD aneurysm	CABG: LIMA to LAD, RIMA to Cx
6	RCA and LAD aneurysms >8 mm	ND; dense ring calcification on CXR	18 yrs: AMI, EF 20%	CABG: SVGs to LAD and RCA, EF improved to 58%
7	Bilateral brachial artery aneurysms; 8-mm LAD aneurysm; 5-mm Cx aneurysm	100	19 yrs: Claudication R arm; 21 yrs: claudication L arm; 23 yrs: unstable angina	19 yrs: resection R brachial artery aneurysm; 21 yrs: resection L brachial artery aneurysm; 23 yrs: LIMA to LAD, SVG to RCA
8	30-mm RCA aneurysm; 12-mm LMCA aneurysm; 15-mm LAD aneurysm	1,943	22 yrs: inferior MI	PTCA with clot aspiration RCA aneurysm
9	RCA and LAD aneurysms >8 mm	ND	13 yrs: stenosis on angiography; 22 yrs: failed graft on angiography	13 yrs: CABG with radial artery; 22 yrs: LIMA to LAD, SVG to RCA
10	100% occluded proximal LMCA with 80%-90% stenosis of RCA	8,218	24 yrs: AMI	CABG: LIMA to LAD; RIMA free graft to PDA
11	5-mm LMCA and LAD aneurysms, 6.5-mm RCA aneurysm	ND	29 yrs: severe CHF with EF 15%	Densely calcified LMCA, LAD, and RCA with 95% LAD stenosis; unsuccessful PTCA; cardiac transplantation
12	"Large" LAD aneurysm; 6-mm RCA aneurysm; 4-mm Cx aneurysm; bilateral brachial and femoral artery aneurysms	513	30 yrs: complete occlusion LAD; anterior hypokinesis (EF 50%); bilateral 80%-90% stenosis of common femoral arteries; 99% occlusion of right ostial SFA	Bilateral common femoral endarterectomies with bovine pericardial patch; stent to right SFA
13	Transient dilation of LMCA on initial echocardiography; 29 yrs: unstable angina, 85% LMCA stenosis	666	32 yrs: unstable angina	CABG: LIMA to the LAD, SVGs to diagonal, obtuse marginal and PDA
14	7-mm LAD aneurysm	ND	32 yrs: AMI; 43 yrs: unstable angina	32 yrs: occluded LAD aneurysm, PTCA attempted, unsuccessful; 43 yrs: extension of LAD occlusion proximally, medical management
15	10-mm RCA aneurysm; 8-mm LAD aneurysm; 7-mm Cx aneurysm	ND	33 yrs: IMI; 36 yrs: unstable angina	33 yrs: PTCA of occluded RCA aneurysm; 36 yrs: reocclusion of RCA aneurysm; medical management
16	8-mm LAD aneurysm; 9.5-mm RCA aneurysm	1,451	33 yrs: AMI	PTCA
17	6-mm RCA aneurysm	17	38 yrs: IMI; 38 yrs: unstable angina	38 yrs: PTCA to RCA with DES placement IVUS 2 mo later: IVUS reveals undersized stent in RCA; PTCA and DES for LAD stenosis
18	Proximal "giant aneurysms"	ND	44 yrs: angina	44 yrs: CABG, SVG to RCA; 45 yrs: stenting of SVG due to recurrent angina, total of 16 stents placed
19	Multiple proximal aneurysms	ND	48 yrs: AMI, complete occlusion of RCA	56 yrs: unstable angina, CABG, SVG to LAD; 68 yrs: sudden death, no autopsy performed
20	Proximal RCA aneurysm >8 mm; proximal LAD stenosis	ND	49 yrs: AMI	PTCA with DES placement
21	6-mm RCA aneurysm, 6-mm dilated LAD	0	54 yrs: STEMI	PTCA with aspiration of thrombus and bare-metal stent placement

AMI = acute myocardial infarction; CABG = coronary artery bypass graft; CT = computed tomographic; CV = cardiovascular; Cx = circumflex coronary artery; CXR = chest x-ray; DES = drug-eluting stent; EF = ejection fraction; FFR = fractional flow reserve; IMI = inferior myocardial infarction; IVUS = intravascular ultrasound; L = left; LAD = left anterior descending coronary artery; LIMA = left internal mammary artery; LMCA = left main coronary artery; ND = not done; PDA = posterior descending artery; PTCA = percutaneous transluminal coronary angioplasty; R = right; RCA = right coronary artery; RIMA = right internal mammary artery; STEMI = ST-segment elevation myocardial infarction; SVG = saphenous vein graft.

FIGURE 2 Intravascular Ultrasound of a 5.5-mm Right Coronary Artery Aneurysm That Was Filled With Thrombus at the Time of Initial Stent Deployment in a 38-Year-Old Vietnamese Man (Patient #17)
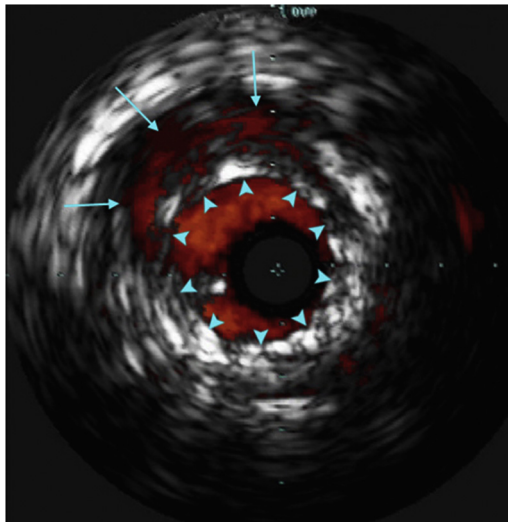
The undersized stent was post-dilated but remained malopposed because of stent-vessel mismatch, with blood flow shown in red **(arrows)** outside of the opaque, white stent wall **(arrowheads)**.

COMPLICATIONS OF CABG. Patient #1 presented at 4 years of age with an inferior MI and underwent CABG approximately 6 h after symptom onset. The right internal mammary artery graft was inadequate in length and was implanted proximal to a distal RCA aneurysm. Subsequent cardiac magnetic resonance imaging performed after the surgery showed an inferior wall that was akinetic with a full-thickness infarct by late enhancement imaging. Another subject (#19) developed angina after CABG following graft thrombosis. He had competitive flow through the aneurysmal native vessel that may have prevented maturation of the saphenous vein graft that thrombosed. One additional subject (#8) who had previously undergone CABG required elective angioplasty for a graft stenosis at the implant site.

CARDIAC TRANSPLANTATION. One subject (#11) developed moderate-sized aneurysms (4 to 6 mm) at the time KD was diagnosed in childhood, followed by remodeling and normalization of the luminal diameter, documented by echocardiography. On that basis he was released from further cardiovascular monitoring. He subsequently required cardiac transplantation for end-stage cardiomyopathy at age 29 years. Prior to transfer for refractory heart failure, PTCA with stent placement was attempted in what proved to be a heavily calcified, stenotic lesion in the LAD. Severely aneurysmal, densely calcified coronary arteries were documented by histopathology following cardiac transplantation (Figures 5A to 5C).

PERIPHERAL VASCULAR INTERVENTIONS. Two patients experienced life-style-limiting claudication of either an upper (#7) or a lower (#12) extremity.

FIGURE 3 Angiogram of 54-Year-Old Filipino Man (Patient #21) Who Presented With an ST-Segment Elevation Myocardial Infarction
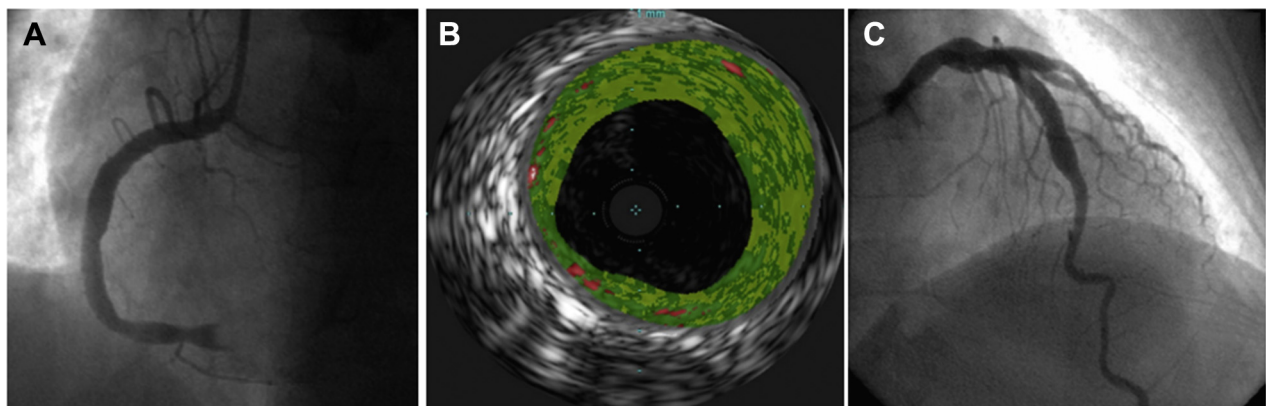
(A) The right coronary artery was diffusely dilated (5 to 6 mm) with thrombus in a distal aneurysm. **(B)** Percutaneous transluminal coronary angioplasty and stenting were performed, with restoration of Thrombolysis In Myocardial Infarction grade 2 flow. IVUS Virtual Histology (Volcano Corporation, San Diego, California) was consistent with layered, organized thrombus and intimal thickening **(green)**, without any changes suggestive of atherosclerosis **(yellow)**. Focal areas of necrosis **(red)** and calcium **(white)** are seen. The blue dots are spaced 1 mm apart, thus giving a luminal measurement of 5 mm in this portion of the aneurysm. **(C)** The proximal left anterior descending coronary artery showed aneurysmal dilation with normal vessel size distally, with no atherosclerotic changes. The aneurysmal dilation of the proximal coronary arteries with normal distal vessels was characteristic of Kawasaki disease (KD), and there was a history of a KD-compatible illness in childhood.

**FIGURE 4   Surgical Resection of an Expanding Giant Aneurysm**
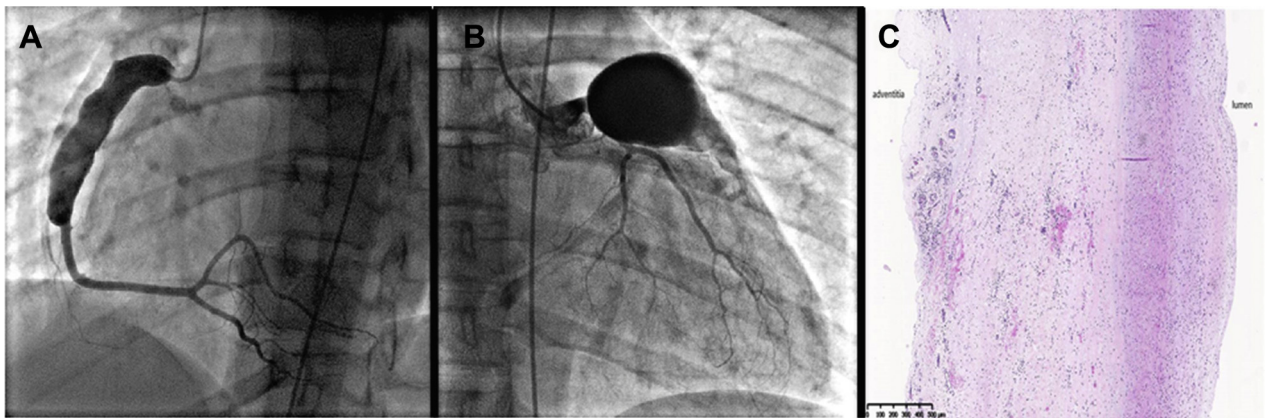
Angiogram of 17-year-old Caucasian woman (Patient #4) with a stable 15-mm right coronary artery aneurysm **(A)** and a progressively enlarging left anterior descending coronary artery aneurysm that measured 7 mm at the time of initial Kawasaki disease diagnosis and 25 mm at the time of surgery 11 years later **(B)**. **(C)**. Histological findings of resected aneurysmal coronary artery wall (hematoxylin and eosin staining, 40×). Vessel wall layers have been replaced by proliferation of spindle-shaped cells with fibroblast/myofibroblast morphology, hyaline degeneration, and proliferation of microvessels. Inflammatory cell infiltration is seen in the adventitia.

Both subjects had developed KD at a very young age, which is a known risk factor for the development of both coronary artery aneurysms and aneurysms in other extraparenchymal, muscular arteries (10,11). Patient #7 underwent 2 separate resection procedures for her brachial artery aneurysms, with resolution of her symptoms (**Figure 6**). For Patient #12, severe, bilateral common femoral artery stenoses were treated successfully with endarterectomy and patch angioplasty with bovine pericardium. A right superficial femoral artery stenosis required stenting.

DISCUSSION

Important principles in management emerged from review of the late cardiovascular sequelae of documented or suspected KD in childhood. Many of the cardiovascular complications resulted from either a failure to initially diagnose and treat acute KD, a delay in treatment at the time of the initial illness in childhood, or a failure to recognize important cardiovascular pathology and provide appropriate longitudinal monitoring. Of note, approximately one-quarter of the subjects in this series had their


FIGURE 5   Explanted Heart With Extensive Arterial Wall Calcification
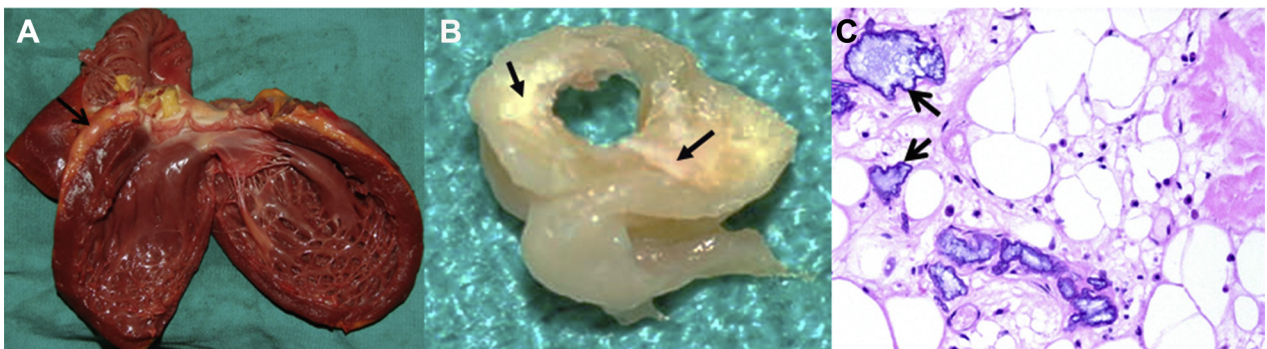
(A) Explanted heart with heavily calcified left anterior descending coronary artery from a 30-year-old Caucasian man (Patient #11). **(B)** Dense calcification in cross section of artery. **(C)** Histological section showing ossification of the arterial wall **(arrows)** with bone marrow elements.

FIGURE 6 Brachial Artery Aneurysm (Arrow) That Required Surgical Resection in a 21-Year-Old Caucasian Woman (Patient #7) With Upper Extremity Claudication
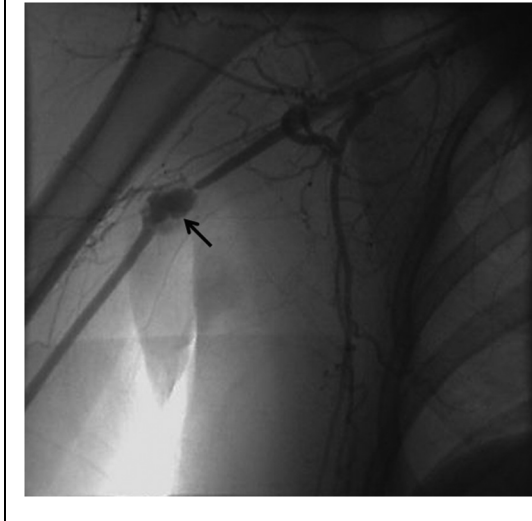
initial KD prior to the advent of effective therapy with intravenous immunoglobulin, which was widely adopted in 1986 following publication of the first U.S. clinical trial (12).

Adverse outcomes of PCI included a failure to appreciate the extent of aneurysmal dilation of a thrombosed artery leading to undersizing of a stent and attempted angioplasty in a heavily calcified artery. Subsequent rethrombosis of a long aneurysmal segment of the RCA despite adequate systemic anticoagulation with warfarin and antiplatelet therapy with aspirin was also observed. Computer modeling has revealed reduced wall shear and increased oscillatory index in these long ectatic segments that predicts a high risk for thrombosis (13). The optimal management of these lesions requires further study, including the role of novel oral anticoagulant agents and creative approaches to deploying drug-eluting stents.

From these cases, we can distill management strategies that may help physicians better serve this growing population of patients. For pediatric cardiologists, the important message is that normalization of the luminal diameter of the vessel does not equate to a structurally normal vessel. Three subjects with known histories of coronary artery abnormalities (#11, #13, and #20) were released from follow-up care by their pediatric cardiologists and experienced potentially life-threatening complications decades later. In a study of 28 young adults in Japan with coronary artery aneurysms after KD, intimal thickening (>0.4 mm) was documented by IVUS in 90% of

vessels in which there had been aneurysms of at least 4 mm at the time of acute KD (14). Autopsy studies have conclusively shown that aneurysms result from a destruction of the vessel wall architecture that is unlikely to normalize (15). A reasonable conclusion from these data would be that all patients with aneurysms of any size resulting from acute KD in childhood carry a lifelong risk for subsequent stenosis and/or thrombosis and deserve longitudinal monitoring by a pediatric cardiologist, with appropriate transition of care to an adult cardiologist knowledgeable about the potential late cardiovascular sequelae in this patient population.

For adult cardiologists, it must be stressed that KD should be considered in the differential diagnosis of myocardial ischemia, infarction, or congestive heart failure in any young adult. For interventional cardiologists specifically, at the time of catheterization, the presence of proximal, calcified coronary artery aneurysms, without the significant narrowing or irregularity associated with atherosclerosis, should prompt consideration of antecedent KD. Atherosclerotic aneurysms are more likely to be diffuse in nature and to occur in older patients with traditional risk factors. IVUS or optical coherence tomography should be performed to properly size the vessel prior to stent deployment and to assess the characteristics of the vessel wall (16,17). Extensive calcification should be recognized because densely calcified vessels may not be dilatable by angioplasty or successfully stented unless pre-treated with rotational atherectomy (18,19). Interview of the patient's parents may uncover a history of a KD-compatible illness in childhood.

Longitudinal outcome data in adults following KD are beginning to emerge from Japan (20-24). One series of 190 patients documented progressive coronary artery stenosis in 58% of 85 adults with moderate aneurysms (6 to 8 mm) and 74% of 121 adults with large aneurysms (>8 mm) 15 years following disease onset (20). Adult cardiologists will be facing a growing population of patients presenting with complications of their KD in childhood with no established guidelines for their care.

Single-center experience with cardiovascular sequelae of KD in adulthood in the United States is limited. The sparse body of research addressing interventional management of KD consists largely of case reports and small case series from Japan (22,24-26). Our series illustrates the spectrum of cardiovascular sequelae that require intervention in young adults who had KD in childhood. Of the 63 cohort 1 subjects followed at our center since the time of KD diagnosis, only 1 (#1) had an acute cardiovascular event treated with an urgent

intervention. However, the mean age of our cohort 1 subjects is currently only 22.1 years (range: 15.0 to 31.7. years). The majority of acute events in subjects in our study occurred in the third to fifth decades of life. Thus, it is likely that additional cohort 1 subjects will experience cardiovascular events as they age. In a midterm follow-up study of 546 subjects with KD followed for an average of 14.9 years in the Kaiser Permanente system, only 2 patients had cardiovascular events after age 15 years (27). Thus, longer term follow-up is needed to more completely describe the event-free survival rate in adults after KD in childhood.

The experience with CABG in this series was largely favorable. However, patient #19 had competitive blood flow through the aneurysms that may have led to thrombosis of his graft. PCI coupled with pharmacological management of thrombosis may be more appropriate in the setting of unstable angina or MI if there is the potential for competitive flow. CABG for aneurysms without significant localized stenosis should be avoided (28). Patient #1 underwent CABG with a right internal mammary artery graft to the distal RCA, but the internal mammary artery was too short to allow implantation beyond a distal RCA aneurysm. Therefore, selection of the artery for grafting should include consideration of the gastro-epiploic artery to bypass very distal aneurysms. Kitamura in Japan has published his experience in 114 pediatric patients with both arterial and venous CABG, who had a 95% survival rate and a 60% cardiac event-free rate at 25 years after surgery (29). Overall, the 20-year graft patency rate was 87% for internal mammary artery grafts (n = 154) and 44% for saphenous vein grafts (n = 30). Thus, although survival rates were good, this population requires close monitoring for late cardiovascular events.

STUDY LIMITATIONS. We recognize both strengths and limitations to this study. This is the first Western report of a series of cardiovascular complications in adults following documented or presumed KD in childhood. However, the observational nature of our study precludes our being able to draw conclusions about the impact of therapies or management approaches in this population. Best practices can be established only through the longitudinal study of large numbers of subjects with KD or through prospective studies, and guidelines are needed to structure the management of this growing patient population. An additional limitation of our study is the presumptive diagnosis of KD in 10 of the subjects. Until the etiology of KD is established, there will continue to be some measure of uncertainty in the diagnosis of all patients diagnosed by clinical criteria that can overlap with other childhood illnesses.

CONCLUSIONS

The diagnosis of antecedent KD should be considered in any young patient presenting with angina or acute MI. A history of KD or a KD-compatible illness in childhood should alert the cardiologist to be prepared for the unique interventional challenges of the coronary artery lesions in this patient population.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. John B. Gordon, San Diego Cardiac Center, 3131 Berger Avenue, San Diego, California 92123. E-mail: jgordon552@mac.com.

PERSPECTIVES

WHAT IS KNOWN? Patients who experienced coronary artery damage from KD in childhood may have vascular complications in adulthood, but the nature of these problems and their management has not been documented in non-Asian populations.

WHAT IS NEW? Adults with aneurysms following KD in childhood require lifelong follow-up with monitoring for the development of ischemia due to coronary artery and peripheral artery stenosis or thrombosis and congestive heart failure due to myocardial fibrosis.

WHAT IS NEXT? Broader awareness of the unique problems encountered in this patient population and systematic tracking of patient outcomes as this population ages will be essential to improve outcomes and define the natural history of this disease into adulthood.

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