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ORIGINAL RESEARCH

Pathological Alterations of Coronary Arteries Late After Kawasaki Disease

An Optical Coherence Tomography Study

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ABSTRACT

BACKGROUND The long-term impact of Kawasaki disease on coronary arteries in vivo is unclear.

OBJECTIVES The purpose of this study was to investigate coronary arteries in the late convalescent phase, we followed patients with Kawasaki disease who developed coronary artery aneurysms (CAAs).

METHODS We followed 24 patients and used optical coherence tomography at a median of 16.6 years after the onset of Kawasaki disease.

RESULTS Of 72 coronary arteries, optical coherence tomography was performed on 61 arteries: 17 with a persistent CAA, 29 with a regressed CAA, and 15 without a CAA. Between-group comparison was performed by chi-square or Fisher's exact test, and intimal thickening (17 vs 29 vs 15, all 100%, P = NA) and medial disruption (17 [100%] vs 29 [100%] vs 14 [93%], $P = 0.25$) were commonly observed in the investigated arteries. Advanced features of atherosclerosis were more frequently seen in arteries with persistent CAAs than in those with regressed CAAs and in those without CAAs: calcification (12 [71%] vs 5 [17%] vs 1 [7%], $P < 0.001$), microvessels (12 [71%] vs 10 [35%] vs 4 [27%], $P = 0.020$), cholesterol crystals (6 [35%] vs 2 [7%] vs 0 [0%], $P = 0.009$), macrophage accumulation (11 [65%] vs 4 [14%] vs 4 [27%], $P = 0.002$), and layered plaque (8 [47%] vs 11 [38%] vs 0 [0%], $P = 0.004$).

CONCLUSIONS Long after onset of Kawasaki disease, all arteries showed pathological changes. Arteries with persistent CAAs had more advanced features of atherosclerosis than those with regressed CAAs and those without CAAs. (JACC Adv 2024;3:100937) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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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.

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ABBREVIATIONS AND ACRONYMS

ASCVD = atherosclerotic cardiovascular disease

CAA = coronary artery aneurysm

OCT = optical coherence tomography

TCFA = thin-cap fibroatheroma

Kawasaki disease is a systemic inflammatory disease that predominantly affects infants and young children. Medium-sized arteries, especially coronary arteries, are likely to be involved, and coronary artery aneurysms (CAAs) are one of the major consequences of the disease that predispose patients to risk of myocardial infarction or sudden cardiac death. Once CAAs have developed, they remain without regression in about 30% of the cases, and persistent CAAs pose a life-long risk of thrombosis beyond childhood.[1,2] Flow turbulence in cavernous CAAs is thought to cause the thrombosis, but atherosclerotic changes in the vessel walls have been reported in the convalescent phase of Kawasaki disease and they might also contribute to the cardiovascular events.[3] Given the rise in newly diagnosed cases of Kawasaki disease, there is presumably a substantial number of adult patients who carry these pathological conditions, which could be an issue when following and treating adult patients with a history of Kawasaki disease.[4]

Optical coherence tomography (OCT) is a form of intravascular imaging with high resolution that facilitates detailed investigation of coronary arteries in vivo. OCT enables visualization of microstructures of coronary arteries that was only previously possible by posthumous microscopic examination.[5,6] A pathological study reported atherosclerotic findings such as cholesterol crystals, macrophage infiltrations, and thrombosis in coronary arteries in autopsy cases of individuals with Kawasaki disease and whom died late after the onset of the disease.[3] The study also showed that these abnormalities were prevalent not only in coronary arteries with CAAs but also in those without CAAs. In vivo investigation of the coronary arteries late after Kawasaki disease with the use of OCT has been limited. This study aims to explore pathological changes of coronary arteries in the late convalescent phase of Kawasaki disease.

METHODS

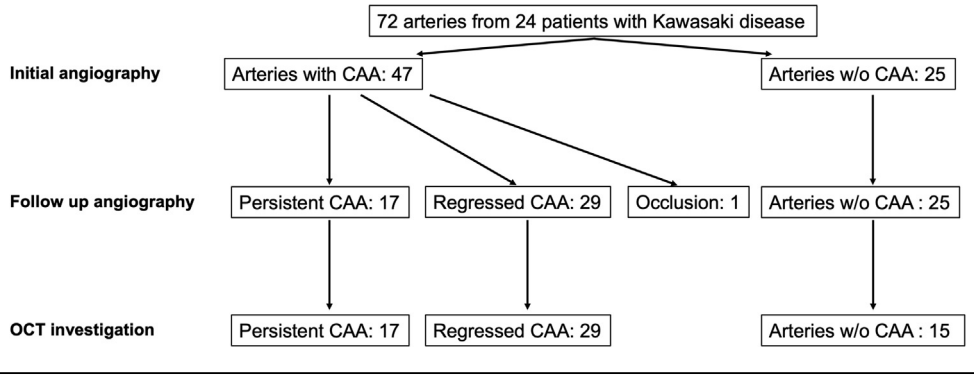
STUDY POPULATION. In this retrospective observational study, patients with Kawasaki disease who developed a CAA in at least one of the major coronary arteries and who underwent OCT investigation during the convalescent phase were consecutively enrolled at the Wakayama Medical University Hospital, Japan. They each underwent invasive coronary angiography for assessment of the coronary artery trees in the acute and follow-up phases, in accordance with the Japanese Kawasaki disease guidelines which recommend regular follow-up of patients who have had CAAs using coronary imaging at 1- to 5-year interval or when leaving high school (usually at the age of 18 years).[4] OCT was performed at the time of the follow-up angiography (**Figure 1**). All the patients provided written informed consent before the cardiac catheterization and OCT. The patients received intravenous immunoglobulin in the acute phase and thromboprophylaxis in the acute phase and until the follow-up phase according to clinical indication. The selection and doses of these treatments were at the discretion of treating physicians. We gathered information on patient characteristics by reviewing electric medical records which included age, sex, height, weight, dates of the onset of Kawasaki disease and invasive cardiac catheterization, and medications. This study complies with the Declaration of Helsinki and has been approved by the Wakayama Medical University Hospital Institutional Ethics Committee (IRB No. 3772). Written informed consent was waived for this study.

ANGIOGRAPHY. Coronary angiography was performed with 5- or 6-F catheters in a standard manner via trans-radial or transfemoral approach. Angiographic images were obtained from multiple projections after administration of intracoronary isosorbide dinitrate. Quantitative coronary angiography analysis was performed using validated quantitative coronary angiography software (CASS II, Pie Medical) and the maximum inner diameter of the coronary arteries was measured.

Z-SCORE. Z-scores of coronary arteries were calculated using a web-based calculator (Z Score Project). The inner diameters of coronary arteries were measured by echocardiography, but those measured by angiography were used if coronary arteries were not visible by echocardiography, particularly in the follow-up phase. If coronary arteries had a lesion with the Z-score of $\geq$2.5, the lesion was deemed as having a CAA. Depending on whether or not the CAA was present in the acute and the follow-up phases, coronary arteries were classified into three groups: arteries with a persistent CAA, those with a regressed CAA, and those without a CAA.

OCT IMAGING. OCT images were acquired with the standard nonocclusive technique with the frequency-domain OCT system (ILUMIEN C7-XR or OPTIS) and Dragonfly imaging catheter (Dragonfly Duo or OPTIS, Abbott). Coronary arteries with a persistent CAA, a regressed CAA, and without a CAA were investigated and assessed qualitatively in terms of the presence of intimal thickening, medial disruption, lipid-rich

FIGURE 1 Study Flow Chart



CAA = coronary artery aneurysm; OCT = optical coherence tomography.

plaque, thin-cap fibroatheroma (TCFA), calcification, microvessel, thrombus, cholesterol crystal, macrophage accumulation, lotus root appearance, and layered plaque. The definitions of these pathological characteristics were in line with those in the literature.[5] Briefly, 'intimal thickening' was defined as high backscattering and relatively homogenous tissues with the thickness of >400 μm (**Figure 2** A5 and A6). 'Medial disruption' was disappearance of the tunica media (**Figure 2** A5 and A6). 'Lipid-rich plaque' was a signal-poor region with a poorly defined or diffuse border with the arc of >90°. 'TCFA' was a lipid-rich plaque with a fibrous cap thickness of <65 μm. 'Calcification' was a signal-poor or heterogeneous region with a sharply delineated border (**Figure 3** A3). 'Microvessel' was a signal-poor sharply delineated tubuloluminal structure (**Figure 3** A4). A 'thrombus' was a mass attached to the luminal surface or floating within the lumen. 'Cholesterol crystals' were thin and linear regions with high intensity (**Figure 3** B2). 'Macrophage accumulation' was signal-rich, and distinct or confluent punctuate regions with shadowing (**Figure 3** A2). 'Lotus-root appearance' was a structure with multiple intraluminal channels separated by high backscattering tissue (**Figure 3** D2).[7] 'Layered plaque' was a region with one or more layers showing different densities from underlying components and a clear border (**Figure 3** C2).[8]

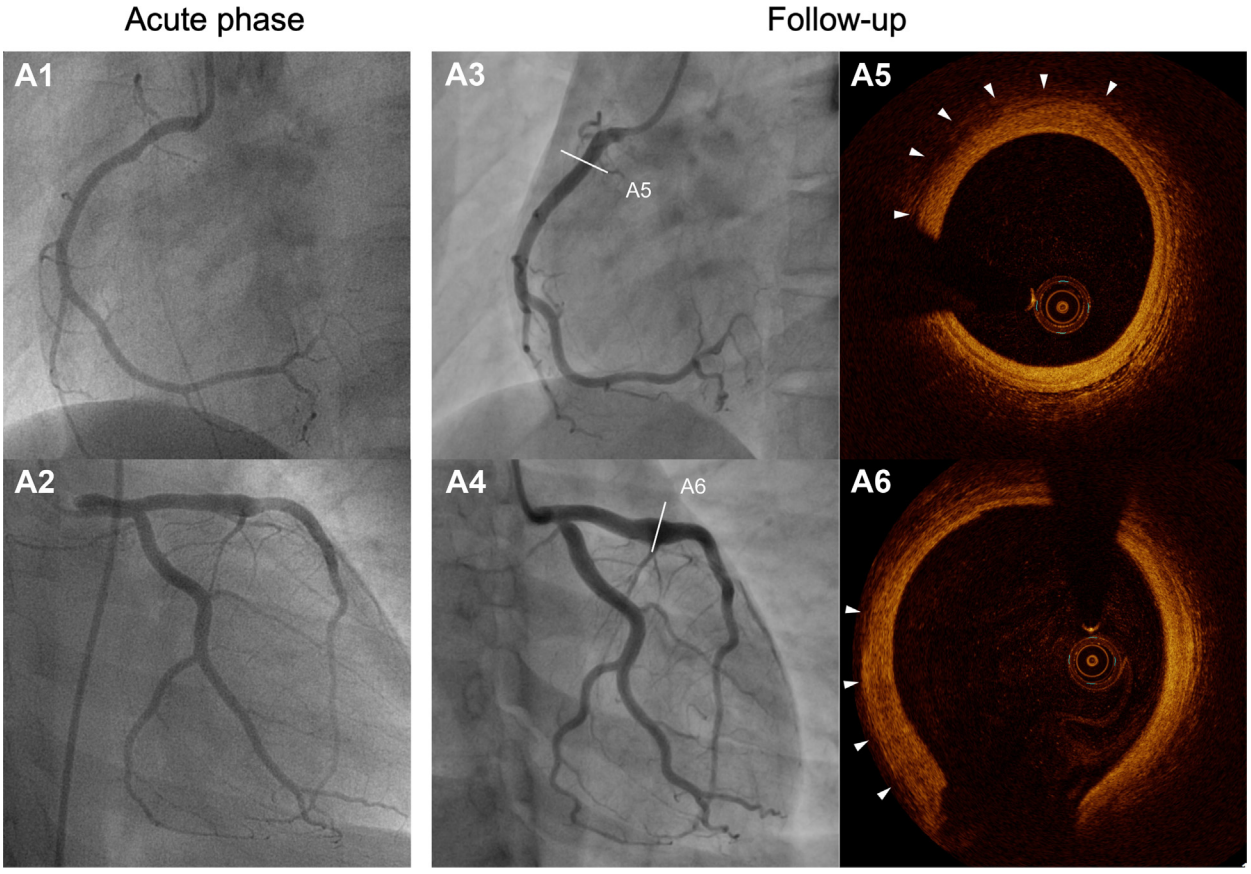
STATISTICAL ANALYSIS. Categorical variables were expressed as numbers (percentages), with comparison by chi-square or Fisher's exact tests as appropriate. Continuous variables were expressed as median (IQR) as they were not normally distributed and were compared using Kruskal-Wallis tests. When overall significance was found in the three-group comparisons, post hoc pairwise tests followed with Bonferroni correction. *P* values were 2-sided, and *P* values <0.05 were considered to be statistically significant. Statistical analyses were performed using R version 4.0.3 (R Foundation).

RESULTS

PATIENT CHARACTERISTICS. We followed 24 patients with Kawasaki disease who developed a CAA in at least one of their major coronary arteries. The median age of the onset of the disease was 1.2 (IQR: 0.5-5.1) years. Intravenous immunoglobulin was given to 22 (92%) patients, aspirin to 24 (100%), and warfarin to 7 (29%) in the acute phase, and 14 (58%) patients were still taking aspirin and 6 (25%) were taking warfarin at the time of the follow-up angiography. During the follow-up, two patients had myocardial infarction within 1 month after the onset. Both patients were medically treated at first, and one of them underwent bypass surgery thereafter. Initial invasive angiography was performed at the median age of 1.5 (IQR: 0.8-5.4) years, and follow-up angiography and OCT were performed at the median age of 18.4 (IQR: 17.9-22.1) years (**Table 1**).

LESION CHARACTERISTICS. We evaluated 72 arteries from the 24 patients, 47 of which showed a CAA and 25 did not show a CAA on the initial angiography. Of the 47 arteries that showed CAAs at the initial angiography, the CAAs remained in 17 arteries, regressed in 29 arteries, and occluded in one artery, which was later surgically revascularized. None of the 25 coronary arteries that had not shown a CAA in the initial angiography showed a newly developed CAA on the follow-up angiography (**Figure 1**). The

FIGURE 2 Pathological Changes in Arteries With and Without a CAA



The LAD developed a CAA, whereas the RCA was not seemingly affected by a CAA (A1, A2) in the acute phase. In the late convalescent phase, the CAA in the LAD remained and the RCA appeared still unaffected (A3, A4). OCT revealed disruption of tunica media and thickened intima (arrowheads) both in the RCA without a CAA and the LAD with the CAA (A5, A6). CAA = coronary artery aneurysm; LAD = left anterior descending artery; OCT = optical coherence tomography; RCA = right coronary artery.

persistent CAAs and the regressed CAAs were more frequently observed in right coronary artery and left anterior descending artery than in left circumflex. Arteries with persistent CAAs had larger Z-score than arteries with regressed CAAs and those without CAAs in the acute phase (7.44 [(IQR: 5.77-8.08)] vs 5.92 [(IQR: 4.36-6.88)] vs 1.28 [(IQR: −0.20 to 1.62)], $P < 0.001$) as well as in the follow-up phase (6.18 [(IQR: 4.44-8.14)] vs 0.93 [(IQR: 0.19-1.56)] vs 0.69 [(IQR: 0.34-1.26)], $P < 0.001$) (Table 2).

OCT FINDINGS. All the arteries with persistent CAAs (n = 17) and regressed CAAs (n = 29) except for the one occluded artery, and 15 out of 25 arteries without CAAs were investigated by OCT (Figure 1). Intimal thickening (17 [100%] vs 29 [100%] vs 15 [100%], P = NA) and medial disruption (17 [100%] vs 29 [100%] vs 14 [93%], $P = 0.25$) were commonly observed in all the investigated arteries. One coronary artery, in the patient who had myocardial infarction, had lotus-root appearance (Figure 3 D). Lipid-rich plaque (0 [0%] vs 2 [7%] vs 1 [7%], $P = 0.60$) was rarely observed, and no arteries showed TCFA. Calcification (12 [71%] vs 5 [17%] vs 1 [7%], $P < 0.001$), microvessels (12 [71%] vs 10 [34%] vs 4 [27%], $P = 0.020$), cholesterol crystal (6 [35%] vs 2 [7%] vs 0 [0%], $P = 0.009$), and macrophage accumulation (11 [65%] vs 4 [14%] vs 4 [27%], $P = 0.002$), were significantly more frequent in arteries with persistent CAAs than those with regressed CAAs and those without CAAs. Also, layered plaque (8 [47%] vs 11 [38%] vs 0 [0%], $P = 0.004$) was more frequent in arteries with persistent or regressed CAAs than those without CAAs (Central Illustration).

DISCUSSION

The main findings of this study were that coronary arteries with persistent CAAs had more advanced atherosclerotic features than those with regressed CAAs and those without CAAs in the late convalescent phase of Kawasaki disease. Secondly, even coronary arteries that had not been affected by CAAs in the acute phase were not healthy, but all those arteries presented with pathological changes: intimal thickening and medial disruption late after the disease. Lastly, nearly 40% of the coronary arteries with CAAs, whether regressed or persisted, showed layered plaque, suggesting frequent occurrence of subclinical thrombosis in those vessels.

ATHEROSCLEROSIS IN CORONARY ARTERIES WITH CAAs. CAA is a well-known and concerning sequelae in patients with Kawasaki disease. Patients with CAAs are at risk of myocardial infarction and sudden cardiac death subsequent to the thrombosis. These life-threatening events are most likely to occur within 2 years after the onset of Kawasaki disease,[9,10] but if CAAs remain after that period, the risk is lifelong. To prevent such complications, antiplatelets and anticoagulants are usually given for thromboprophylaxis because the stasis of the flow in the CAAs is thought to be the cause of the thrombosis. In the present study, however, coronary arteries that had been affected by CAAs presented with characteristics of advanced atherosclerosis: calcifications, microvessels, cholesterol crystals, and macrophage accumulation. These characteristics are known to be indicative of plaque vulnerability.[11] Cardiovascular events might therefore occur from these atherosclerotic lesions in addition to CAAs themselves in the late convalescent phase of Kawasaki disease.

Previous studies using intravascular ultrasound or virtual histology reported atherosclerotic changes in coronary arteries that had been affected by CAAs late after Kawasaki disease.[12,13] In these studies, thickened intima, fibrous tissues, fibrofatty tissues, dense calcium, and necrotic tissues were documented in patients with CAAs. This current study provides more detailed in vivo-based information with regard to microstructural alterations of coronary arteries late after Kawasaki disease, which has only previously been reported by a histology study,[3] by virtue of the high resolution of OCT.

PAN-VASCULITIS IN KAWASAKI DISEASE. Intimal thickening and medial disruption were commonly observed in coronary arteries, irrespective of whether the coronary arteries had been affected by CAAs. We previously reported that intimal thickening and

FIGURE 3 Atherosclerotic Changes Detected by OCT in Arteries With a CAA

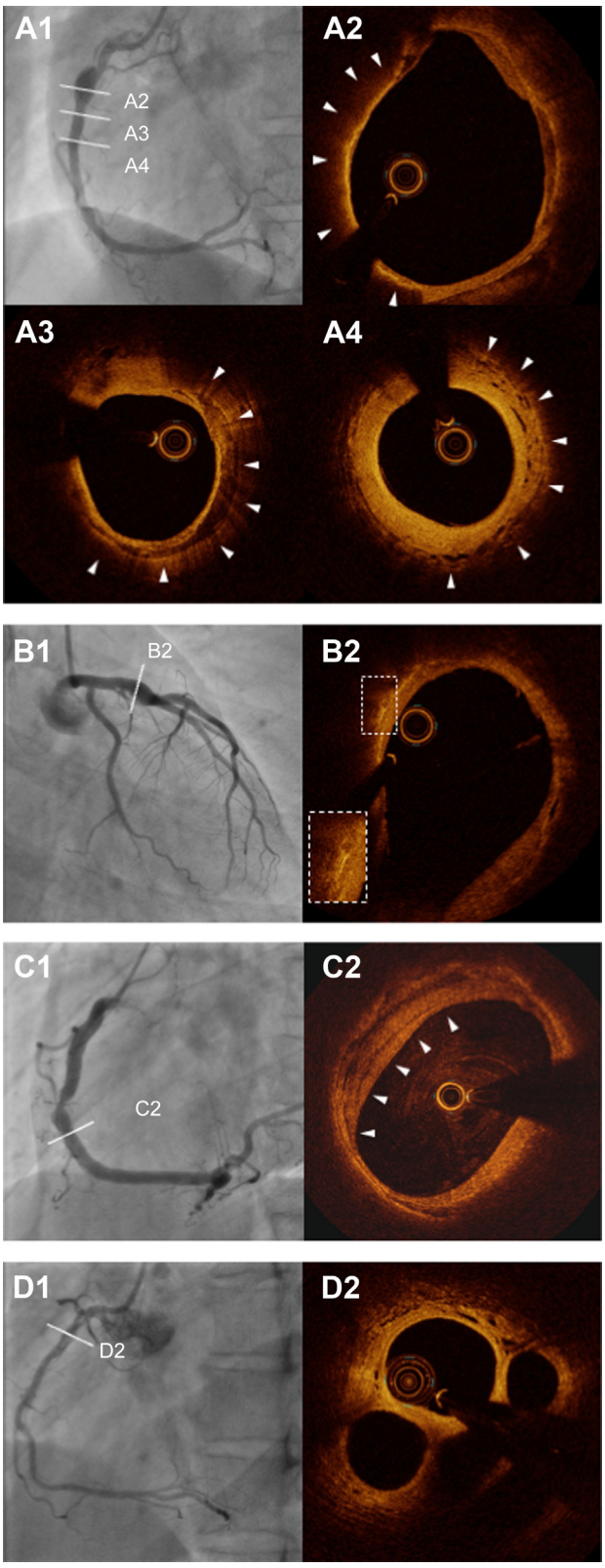


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TABLE 1 Patient Characteristics (N = 24)

Age at the onset of KD, y	1.2 (0.5-5.1)
Age at the time of initial angiography, y	1.5 (0.8-5.4)
Age at the time of follow-up, y	18.4 (17.9-22.1)
Duration between the onset and the first angiography, y	0.2 (0.1-0.3)
Duration from the onset to the second angiography, y	16.6 (12.2-18.7)
Male	19 (79)
Medication at the acute phase	
Aspirin	24 (100)
Warfarin	7 (29)
IVIG treatment	22 (92)
Medication at follow-up	
Aspirin	14 (58)
Warfarin	6 (25)

Values are n (%) or median (IQR).
IVIG = intravenous immunoglobulin; KD = Kawasaki disease.

medial disruption were observed in coronary arteries that had never been affected by CAA as well as in those with regressed CAAs.[14] Other OCT and autopsy studies showed thickened intima in unaffected arteries as well as in those affected by CAAs in the convalescent phase of Kawasaki disease.[3,15,16] The median age at the time of OCT was 18.4 (IQR: 17.9-22.1) years in our study population, so it is reasonable to suggest that these abnormalities should be attributed to Kawasaki disease rather than to the general process of atherosclerosis, despite the limited data available on normal findings of coronary vessel wall layers in children and young adults.[16,17] These findings suggest Kawasaki disease involves not only coronary arteries that develop CAAs but also those that appear seemingly unaffected by CAAs on echocardiography or angiography. Given the nature of Kawasaki disease as a systemic inflammatory disease that can involve medium-sized arteries other than the coronary arteries,[18] it is understandable that the disease affects the entire coronary system.

FIGURE 3 Continued

An RCA presented with a persistent CAA (A1), and OCT images showed macrophage accumulation (arrowheads in A2), calcification (arrowheads in A3), and microvessels (arrowheads in A4). The LAD with a persistent CAA (B1). Cholesterol crystal was identified by OCT at the segment with the CAA (dashed rectangle in B2). The RCA showed a small CAA with stenosis in the middle segment (C1) and OCT showed layered plaque at the distal segment to the CAA (arrow heads in C2). The RCA showed filling defect with haziness in the proximal segment (D1) and lotus-root appearance was revealed in the same segment by OCT (D2). CAA = coronary artery aneurysm; LAD = left anterior descending artery; OCT = optical coherence tomography; RCA = right coronary artery.

Although CAAs draw attention in Kawasaki disease, pathological changes in seemingly unaffected arteries as well as atherosclerotic changes, as mentioned above, should be considered when patients with a history of Kawasaki disease are followed. As these pathological changes were found in coronary arteries of young adults, they might be more likely to develop coronary artery disease as they grow and are exposed to risk factors such as hypertension, diabetes, and dyslipidemia compared with the general population. Preventive measures usually applied for atherosclerotic cardiovascular disease (ASCVD) might also be reasonable for patients in the convalescent phase of Kawasaki disease, although this still requires elucidation.

THROMBOSIS IN KAWASAKI DISEASE. Layered plaque is thought to be a trace of thrombosis and is often detected in coronary arteries in patients with ASCVD.[8,19] In this study, layered plaques were also found in coronary arteries in the late convalescent phase of Kawasaki disease. We propose that layered plaques in Kawasaki disease also suggest a previous intracoronary thrombosis as they do in ASCVD.

Layered plaques were most often found in coronary arteries with persistent CAAs, which were followed by those with regressed CAAs, but they were not identified in arteries that had never been affected by CAAs at all. CAA is thus suggested to be the strongest factor related to coronary thrombosis in Kawasaki disease. Although only two patients had myocardial infarction in our study, layered plaques were found more often: 19 out of 46 coronary arteries with either persistent or regressed CAAs showed layered plaques. Coronary thrombotic events had likely happened subclinically in those cases and they might have prevented development into clinically overt myocardial infarction because more than half of the patients in this study were taking thromboprophylaxis. These findings justify the antithrombotic therapy in cases with CAAs which is recommended by the guidelines of Kawasaki disease.[4]

CORONARY IMAGING IN KAWASAKI DISEASE. The role of coronary imaging is imperative in the detection, evaluation, and follow-up of patients with the consequences of Kawasaki disease. Invasive and noninvasive methods are used for these purposes. The former includes coronary angiography, intravascular ultrasound, and OCT, while the latter includes echocardiography, computed tomography angiography, and magnetic resonance angiography. Currently, the choice of modalities to assess coronary arteries in Kawasaki disease is left to the discretion of

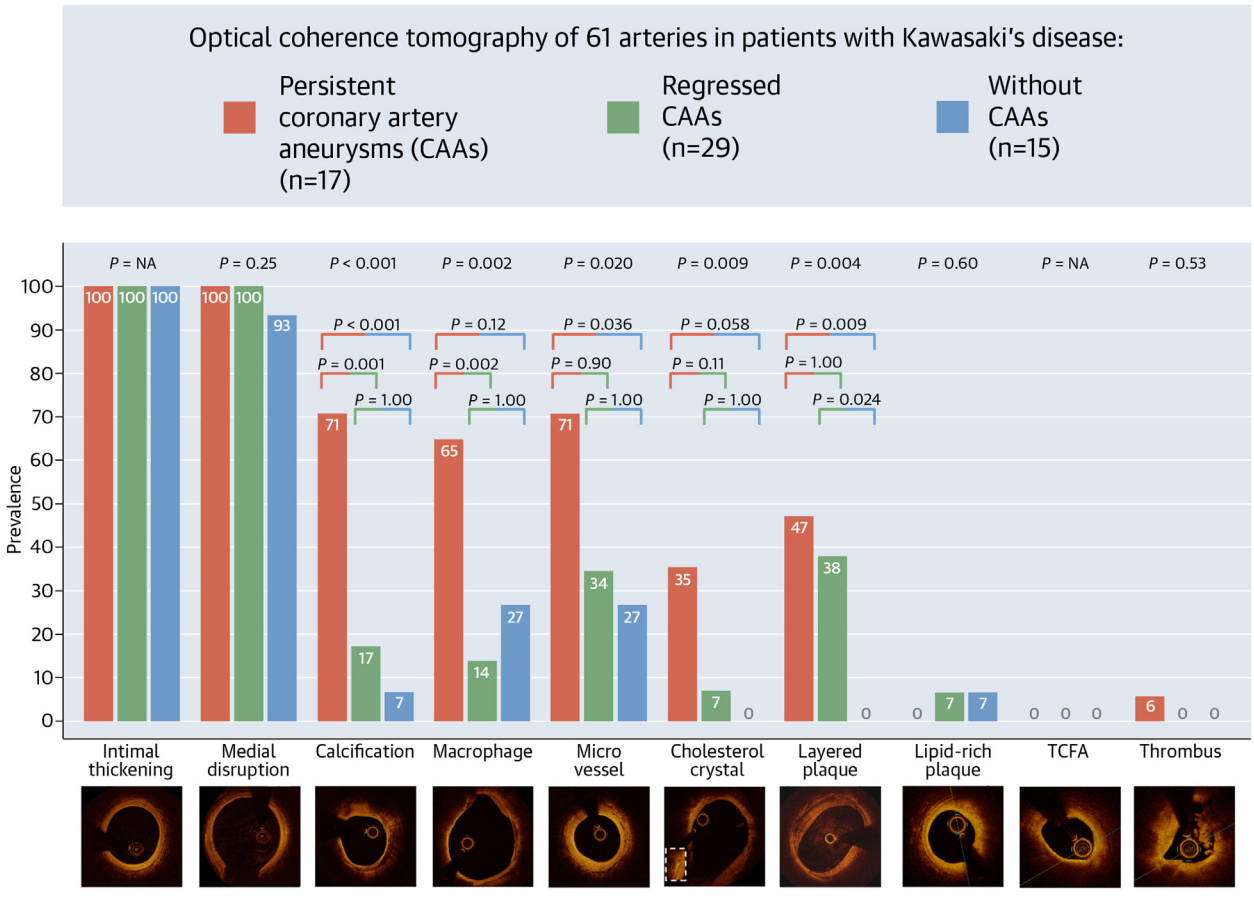
TABLE 2 Lesion Characteristics

	Arteries With Persistent CAAs (n = 17)	Arteries With Regressed CAAs (n = 29)	Arteries Without CAAs (n = 25)	*P* Value
Vessels				<0.001
RCA	7 (41)	14 (48)	3 (12)	
LAD	6 (35)	13 (45)	4 (16)	
LCX	4 (24)	2 (7)	18 (72)	
Vessel diameter in the acute phase, mm	6.60 (5.70-7.40)[ab]	4.00 (3.55-4.89)[c]	2.00 (1.71-2.30)	<0.001
Z-score in the acute phase	7.44 (5.77-8.08)[a]	5.92 (4.36-6.88)[c]	1.28 (−0.20 to 1.62)	<0.001
Vessel diameter in the follow-up phase, mm	6.78 (5.54-7.60)[ab]	3.38 (3.08-3.67)[c]	3.07 (2.62-3.28)	<0.001
Z-score in the follow-up phase	6.18 (4.44-8.14)[ab]	0.93 (0.19-1.56)	0.69 (0.34-1.26)	<0.001

Values are n (%) or median (IQR). Z-scores of coronary arterial internal diameters were calculated using a web-based calculator (Version 4.0 Full, LMS_Z_Score). [a]$P < 0.05$ after Bonferroni correction in the post hoc pairwise comparison between arteries with persistent CAAs and arteries without CAAs. [b]$P < 0.05$ after Bonferroni correction in the post hoc pairwise comparison between arteries with persistent CAAs and arteries with regressed CAAs. [c]$P < 0.05$ after Bonferroni correction in the post hoc pairwise comparison between arteries with regressed CAAs and arteries without CAAs.

CAA = coronary artery aneurysm; LAD = left anterior descending artery; LCX = left circumflex; RCA = right coronary artery.

CENTRAL ILLUSTRATION Prevalence of Pathological Coronary Arteries Late After Kawasaki Disease Using Optical Coherence Tomography



Shiono Y, et al. JACC Adv. 2024;3(6):100937.

Red, green, and blue bars represent the prevalence of each abnormal plaque characteristic between arteries with CAAs, those with regressed CAAs, and those without CAAs, respectively. Pairwise tests results with Bonferroni correction are shown where statistical significance is found in 3-group comparisons. CAA = coronary artery aneurysm; TCFA = thin-cap fibroatheroma.

physicians, who weigh the advantages and disadvantages of each method. For example, OCT, when used in conjunction with coronary angiography, allows for in vivo visualization of the microstructure of coronary arteries, as seen in this study. However, this comes at the cost of invasiveness and radiation exposure. Computed tomography angiography and magnetic resonance imaging provide visualization of coronary arteries with less invasiveness and radiation exposure, although they have lower resolution compared to invasive angiography and OCT. These noninvasive methods can be considered as alternatives to invasive angiography, particularly for children and young adults, as these patients may require repeated assessments. While current guidelines suggest the indications for each method, many of them lack robust evidence to support their recommendations.[4] The methods for following up with patients suffering from the consequences of Kawasaki disease should be the subject of future research.

STUDY LIMITATIONS. First, it is an observational study with a small sample size from a single institute. However, the number of patients investigated was larger than those of previous studies investigating coronary arteries in the late convalescent phase of Kawasaki disease with use of intravascular imaging including intravascular ultrasound and OCT.[12,13,15,16] Second, the follow-up angiography and OCT were not performed in a scheduled manner, but rather according to clinical indication. Also, the OCT investigations were cross-sectional observations at a single time point. The time course of the evolution of atherosclerosis therefore remains unknown. In addition, the link between coronary artery abnormalities found in OCT and future cardiovascular events remains unknown. A long-term study with a large number of patients is necessary to elucidate the risk of patients with these abnormalities. Third, in case of giant CAAs, the entire structure of the aneurysms was unable to be observed owing to the limited field of view of OCT. In such cases, findings might have been overlooked. Lastly, this study only included patients who had developed CAAs in at least one of the major coronary arteries. Whether our findings can be applied to patients with Kawasaki disease without the development of CAAs remains unknown.

CONCLUSIONS

Late after the onset of Kawasaki disease, intimal thickening and medial disruption were commonly seen in coronary arteries irrespective of CAAs, and coronary arteries with persistent CAAs had more advanced features of atherosclerosis than those with regressed CAAs and those that had never been affected by CAAs.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In an in vivo investigation by OCT, patients who had developed CAAs subsequent to Kawasaki disease in their infancy or childhood had atherosclerotic changes in their coronary arteries in adolescence or young adulthood. In addition, in the coronary arteries affected by CAAs, coronary thrombosis seemed to have occurred more often than clinically recognized.

COMPETENCY IN PATIENT CARE: This study justifies the use of thromboprophylaxis for patients with a history of Kawasaki disease and CAAs and suggests early initiation of preventive measures against atherosclerosis in those patients.

TRANSLATIONAL OUTLOOK: Clinical trials are warranted to assess effectiveness and safety of anti-atherosclerotic medications as well as lifelong thromboprophylaxis in patients with a history of Kawasaki disease.

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