Intimal Thickening and Disruption of The Media Occur in The Arterial Walls of Coronary Arteries Not Associated With Coronary Arterial Aneurysms in Patients With Kawasaki Disease

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Research Article

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Abstract

Background

Coronary artery aneurysm (CAA) is an important complication of Kawasaki disease (KD) that is associated with arterial structure damage. However, few studies have examined structural changes in coronary arteries not associated with CAA.

Methods

We examined coronary arteries in KD patients with CAAs who underwent follow-up coronary angiography (CAG) and optical coherence tomography (OCT). Coronary arterial branches with no abnormal findings on most recent CAG were classified into two groups. Arteries with an acute-phase CAA that later regressed were classified as group R and arteries with no abnormal findings on either acute or convalescent phase CAG were classified as group N. Coronary arterial wall structural changes were compared between groups using OCT.

Results

Fifty-seven coronary arterial branches in 23 patients were evaluated by OCT. Thirty-six branches showed no abnormality on most recent CAG. Both groups R and N comprised 18 branches. Maximum intimal thickness in groups R and N was 475 and 355 μm, respectively ($p = 0.007$). The incidence of disruption of the media was 100% and 67%, respectively ($p = 0.02$). Calcification, macrophage accumulation, and thrombus were not found in either group.

Conclusions

Intimal thickening and disruption of the media occur not only in coronary arteries with acute phase CAAs that later regress in the convalescent phase, but also in arteries with normal CAG findings in the acute and convalescent phases.

Background

Kawasaki disease (KD) is an acute systemic vasculitis that appears most frequently in infants and children. As treatment has improved with intravenous immunoglobulin (IVIG) and other therapies, such as steroids[1)], infliximab[2)], and cyclosporine[3)], the incidence of coronary artery aneurysm (CAA) has decreased to 2.6% according to a 2017–2018 nationwide survey in Japan[4)]. However, the absolute number of patients who develop CAA in Japan has essentially remained the same because the incidence of KD has been increasing. Therefore, preventing development of CAA remains a major clinical concern.

Most CAAs smaller than medium size in the acute phase of KD later regress in the convalescent phase. On ultrasound cardiography (UCG) and selective coronary angiography (CAG), these arteries revert to a normal appearance. However, the vascular structure where the acute CAA had been present is abnormal

because of healing-related intimal thickening[5]. Although many autopsy reports have described structural changes within a dilated coronary artery[5,6], only a few reports have described *in vivo* coronary arterial wall changes in CAAs using intravascular ultrasound (IVUS) and optical coherence tomography (OCT)[7,8,9]. In addition, few reports have evaluated normal coronary arterial branches without CAAs following the acute phase in KD patients evaluated by OCT [9].

Although IVUS has been used to evaluate coronary arterial walls, detailed evaluation is difficult because of its poor resolution (100–200 μm). OCT is a newer intravascular imaging modality that can be used as an alternative[10,11,12]. OCT has a higher resolution (10–20 μm) and can clearly discriminate the three laminar structures (intima, media, and adventitia) of vessel walls. In addition, it can differentiate tissue properties (calcification, adipose tissue, macrophage colonization) within vessel walls in detail. This study used OCT to compare arterial wall structure in coronary branches without CAAs with the structure in branches with CAAs in the acute phase that regressed in the convalescent phase in KD patients with CAAs.

Patients And Methods

2.1. Patients

This retrospective study enrolled KD patients who developed a CAA (inner coronary artery diameter ≥4 mm) on UCG at1 month of disease onset. CAAs were defined according to the 1983 Japanese Ministry of Welfare criteria[13] and confirmed by CAG, which was performed repeatedly in accordance with KD guidelines[14]. In follow-up CAG performed between January 2012 and March 2018, OCT was performed concurrently in patients with bodyweight ≥30 kg. The study was approved by the Wakayama Medical University Ethical Review Board (No. 2916) and conforms with the ethical guidelines of the 1975 Declaration of Helsinki. Written informed consent was obtained from all participants.

2.2. CAG

Bilateral selective CAG was performed. After a 6 Fr sheath was placed in the right radial artery, 5 Fr catheters were advanced to the coronary ostia bilaterally for contrast injection.

2.3. OCT procedure

For OCT, a 6 Fr guiding coronary artery catheter was placed at the origin of each coronary artery to advance a guidewire. A C7 Dragonfly Intravascular Imaging Catheter (0.036-inch outer diameter; St. Jude Medical, Inc. St. Paul, MN, USA) was inserted into the distal coronary artery. The guiding catheter was continuously flushed with contrast medium to remove blood cells from the observation region during OCT scanning. OCT was imaged using an automatic pullback device (20 mm/s) at a frame rate of 100 frames/s and recorded on a C7-XR OCT Intravascular Imaging System (St. Jude Medical, Inc.).

2.4. Evaluation of coronary artery wall structure changes

In coronary arteries in which OCT could be applied, we focused on branches with no dilatation or stenosis on the most recent CAG. Branches were classified into two groups based on CAG findings. Branches that developed CAA in the acute phase that later regressed in the convalescent phase ("normalization") were classified as group R. Those with no abnormal findings in either the acute or convalescent phases were classified as group N. We excluded branches with residual CAA on the most recent CAG from this study, as it is difficult to accurately evaluate the entire circumference of the CAA in these branches on OCT because of insufficient blood cell washout with contrast medium and/or inadequate observational range.

In group R, OCT images of a 10-mm segment of the region that included the acute-phase CAA were extracted at 1-mm intervals. In group N, images were extracted from a 10-mm segment of the origin of each branch, where CAA had never developed. We excluded branches that had imaging artifacts or included a side branch that comprised >25% of the observed region.

2.5. Analysis of OCT images

All OCT imaging data were digitized, transferred to ImageJ (US National Institutes of Health, Bethesda, MD, USA), and analyzed in two-dimensions by 2 observers who were blinded to CAG findings. OCT imaging of the three laminar areas was acquired in a concentric pattern from the vascular lumen to the outside to show the intima, media, and adventitia. Maximum intimal diameter was measured. Intimal cross-sectional area was calculated by subtracting the medial area (i.e., vascular lumen cross-sectional area) from the circumferential medial cross-sectional area; the mean area of the target cross sections was determined **(Figure 1)**.

In previous studies, coronary artery intimal thickness <300 μm was considered normal[7,15,16,17], so we defined thickness >400 μm as abnormal. In addition to intimal thickness and cross-sectional area, disruption of the media, calcification (sharply delineated borders with heterogeneous poor signal composition), macrophage colonization (signal-rich, distinct, and greatly attenuated OCT light), and thrombus (mass attached to the luminal surface or floating within the lumen) were evaluated and compared between groups R and N. All evaluations were made in accordance with the consensus standards for acquisition, measurement, and reporting of OCT studies[18].

2.6. Statistical analysis

Quantitative variables are expressed as medians with range and categorical variables as numbers with percentage. Statistical analyses were performed using the Mann-Whitney U test and the chi-square test in JMP Pro 13 software (SAS Institute Japan, Tokyo, Japan). $P < 0.05$ was considered significant.

Results

3.1. Patient characteristics

Twenty-three patients were included for analysis. Patient characteristics are shown in **Table 1**. Median age of KD onset was 1 year and 2 months. Male: female ratio was 18:5. Twenty-one patients (91%) were treated with IVIG, and 13 (62%) did not respond. As second-line treatment, 4 patients (17%) were treated with steroids and 2 (9%) with cyclosporine. The median interval between KD onset and initial CAG was 2 months. Two patients had an interval longer than 4 months (5 and 13 months, respectively) because of CAA-related myocardial infarction in the early acute phase; the other 21 underwent initial CAG within 3 months. Median age at OCT was 18 years and 2 months. Median interval between KD onset and OCT was 16 years and 9 months. No OCT-related complications occurred.

3.2. Arterial branch characteristics

Among the 23 study patients, a total of 69 coronary arterial branches were examined. However, good-quality OCT images could not be acquired in 12 branches; therefore, 57 branches were analyzed. CAAs were not found on the most recent CAG in 36 branches (63%). Eighteen of these branches were classified as group R (right coronary artery [RCA], 8; left anterior descending coronary artery [LAD], 7; and left circumflex coronary artery [LCX], 3) and 18 as group N (RCA, 6; LAD, 6; and LCX, 9; **Figure 2**).

3.3. Wall structure changes

In group R, OCT showed widespread and considerable intimal thickening with disruption of the media in the region of observation. Unexpectedly, regions of observation in group N showed mild intimal thickening and partial disruption of the media **(Figure 3)**. A summary of UCG and OCT data from both groups is shown in **Table 2**. Median maximum intimal thickness and cross-sectional area of the intima were significantly greater in group R than group N. The incidence of abnormal intimal thickening (>400 μm) and disruption of the media were significantly higher in group R than group N ($p < 0.001$ and $p = 0.02$, respectively). Calcification, macrophage colonization, and thrombus were not found in either group.

Discussion

This study examined coronary arterial wall changes in 23 patients who developed CAA in the acute phase of KD using OCT. We compared structural changes in the three layers of the arterial wall between arterial branches without CAA in either the acute or convalescent phases (group N) and those with CAA in the acute phase that regressed in the convalescent phase (group R). Intimal thickening and (partial) disruption of the media were found in the coronary arterial walls in both groups R and N. To the best of our knowledge, this is the first study to report intimal thickening and disruption of the media in coronary arterial walls damaged by inflammation caused by KD, even in arteries not affected by CAA development using OCT.

Many autopsy studies have reported various arterial wall changes that occur in arterial segments associated with CAA, such as intimal thickening, disruption of the media, and calcification[19]. In addition, these changes are found in arteries where the CAA regressed in the convalescent phase, which resulted in normal arterial appearance on UCG and selective CAG[5].

The 3 layers of the coronary arterial wall (intima, media, and adventitia) can be clearly distinguished using OCT. We found that all group R arterial branches exhibited abnormal intimal thickening (> 400 μm). Tsuda et al.[13] also reported that intimal–medial thickening >400 μm frequently developed in coronary branches that dilated to >4.0 mm diameter within 100 days of KD onset using IVUS. In addition, Dionne et al.[9] reported that average intimal thickness in segments with a CAA was 315 μm in the right coronary artery, 455 μm in the left anterior descending coronary artery and 360 μm in the left circumflex coronary artery.

Abnormal intimal thickening develops in the involved arterial area after CAA regression, although the inner diameter appears normal on echocardiography and CAG. However, endothelial cell function is not normal in these remodeling vessels, as shown by a previous study[20]. Intimal dysfunction in the area of CAA regression may induce local stenosis or arteriosclerosis in the future.

Although the incidence of abnormal intimal thickening (≥400 μm) in coronary arterial branches was lower in group N (39%) than group R (100%), median maximum intimal thickness in group N was 335 μm (range, 118–552), which is significantly greater than normal. These data suggest that KD-related inflammation may affect not only CAA-associated branches, but also those without CAA. Therefore, coronary arterial branches considered even normal in the acute phase may later develop intimal thickening and disruption of the media. Several autopsy studies have reported KD-related inflammatory damage in the walls of coronary arteries not affected by coronary artery lesions [21][22], which supports our findings.

Intimal thickening in coronary arterial branches unaffected by CAA is an important point to discuss. Median maximum intimal thickness in group N in our study was 355 μm; however, Dionne et al. reported 61.7±17 μm[9]. Differences between two studies in the evaluated segments of the coronary arteries may explain this discrepancy. Our study evaluated only a 10-mm segment of the proximal coronary arterial branches in group N, while Dionne et al. did not specify the region of evaluation. We selected a proximal segment for two reasons. First, this area is easily evaluated by OCT, and second, the evaluated segments needed to be equivalent between groups.

In several reports, KD patients with coronary artery lesions that regressed and became normal angiographically developed cardiovascular disorders at a young age [23][24]. Other studies have reported that the coronary arterial wall in segments unaffected by aneurysms has the same abnormal vascular function as segments associated with regressed lesions[25][26][27]. These studies support our findings. Even KD patients with normal appearing coronary arteries in the acute phase may later develop various cardiovascular disorders, similar to patients who develop CAAs that later regress.

Limitations

This study has several limitations. First, several biases were present, such as age of KD onset and interval between KD onset and OCT. These factors were not adjusted for because of the limited number of

patients. Second, we could not perform OCT in KD patients who did not develop CAA because of ethical considerations, so data regarding intimal thickness and disruption of the media in these patients was not collected.

Conclusions

In KD patients, intimal thickening and disruption of the media occur not only in coronary arteries with acute phase CAAs that later regress in the convalescent phase, but also in arteries with normal CAG findings in the acute and convalescent phases. If these changes are associated with healing from KD vasculitis, long-term follow-up of KD patients with and without CAA may be required.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Wakayama Medical University Ethical Review Board (No. 2916). The study protocol conforms with the ethical guidelines of the 1975 Declaration of Helsinki. This retrospective study was based on medical records. We obtained informed consent before catheterization from all patients.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author's Contributions

TT, NK, TS, SS and HS contributed to the study conception and design. Acquisition of data was performed by TT and TS. Analysis of data was performed by YI, TK and TA. Interpretation of data was

performed by TT, NK and HS. The first draft of manuscript was written by TT, and NK, TS, TA and HS substantively revised it. All authors read and approved the final manuscript. HS supervised the project.

Author information (optional)

None.

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Tables

Table 1. Patients characteristics

		(minimum–maximum)
Number of patients	23	
Male : female	18 : 5	
Age at the onset of KD	1 year and 2 months*	(1 month–10 years and 11 months)
Interval between the onset of KD and the first CAG	2 months*	(1 month–1 year and 1 month)
Age at the OCT examination	18 years and 2 months*	(11 years and 1 month–29 years and 3 months)
Interval between the onset of KD and OCT	16 years and 9 months*	(5 years and 1 month–24 years and 4 months)

*Median.

Table 2. Summary of ultrasound cardiography and optical coherence tomography data

	Group R (n = 18)	Group N (n = 18)	p value
CA diameter by UCG 1 month after KD (Z score), median (minimum–maximum)	6.06 (3.03–11.18)	1.64 (-0.96–2.23)	p < 0.001
Maximum intimal thickness (μm), median (minimum–maximum)	475 (386–646)	355 (118–552)	p = 0.007
Number of abnormal intimal thickening (> 400 μm), n (%)	17 (94)	7 (39)	p < 0.001
Cross-sectional area of the intima (mm^2), median (minimum–maximum)	4.12 (2.04–7.86)	2.88 (1.45–5.70)	p = 0.029
Disruption of the media, n (%)	18 (100)	12 (67)	p = 0.020

CA = coronary artery

UCG = ultrasound cardiography

KD = Kawasaki disease

Figures

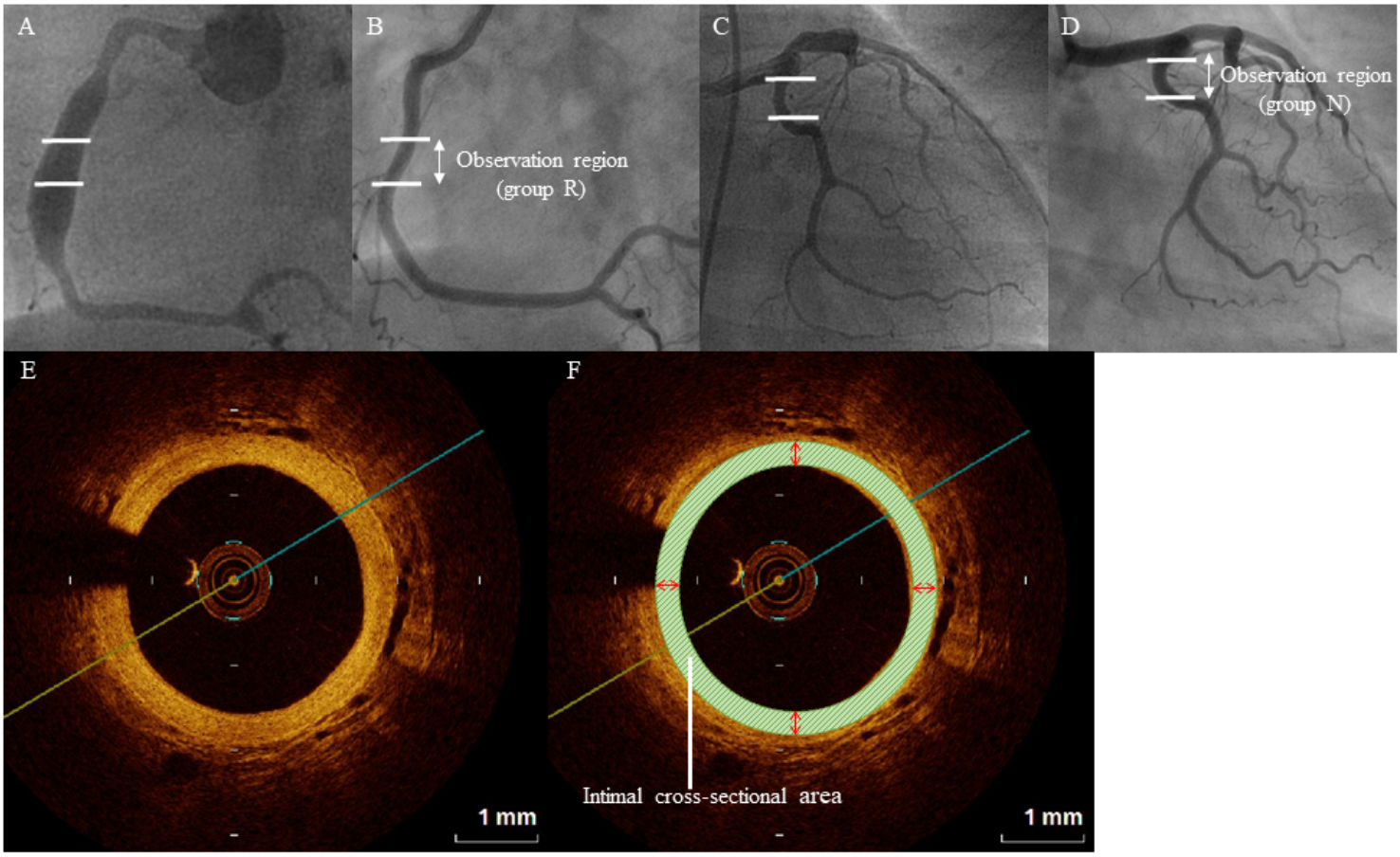

Figure 1

A and B: right coronary angiography (CAG). C and D: left CAG. E and F: Optical coherence tomography (OCT) coronary artery images. (A and B) In group R, we evaluated a 10-mm coronary arterial segment that developed CAA in the acute phase (A) and regressed in the convalescent phase (B). (C and D) In group N, we evaluated a 10-mm segment of the origin of each branch, where there were no abnormal changes in the acute (C) or convalescent (D) phases. (E) OCT image showing disruption of the media and abnormal intimal thickening. (F) We calculated the intimal cross-sectional area by subtracting the medial area (i.e., vascular lumen cross-sectional area) from the circumferential medial cross-sectional area; the mean area of the target cross sections was determined.

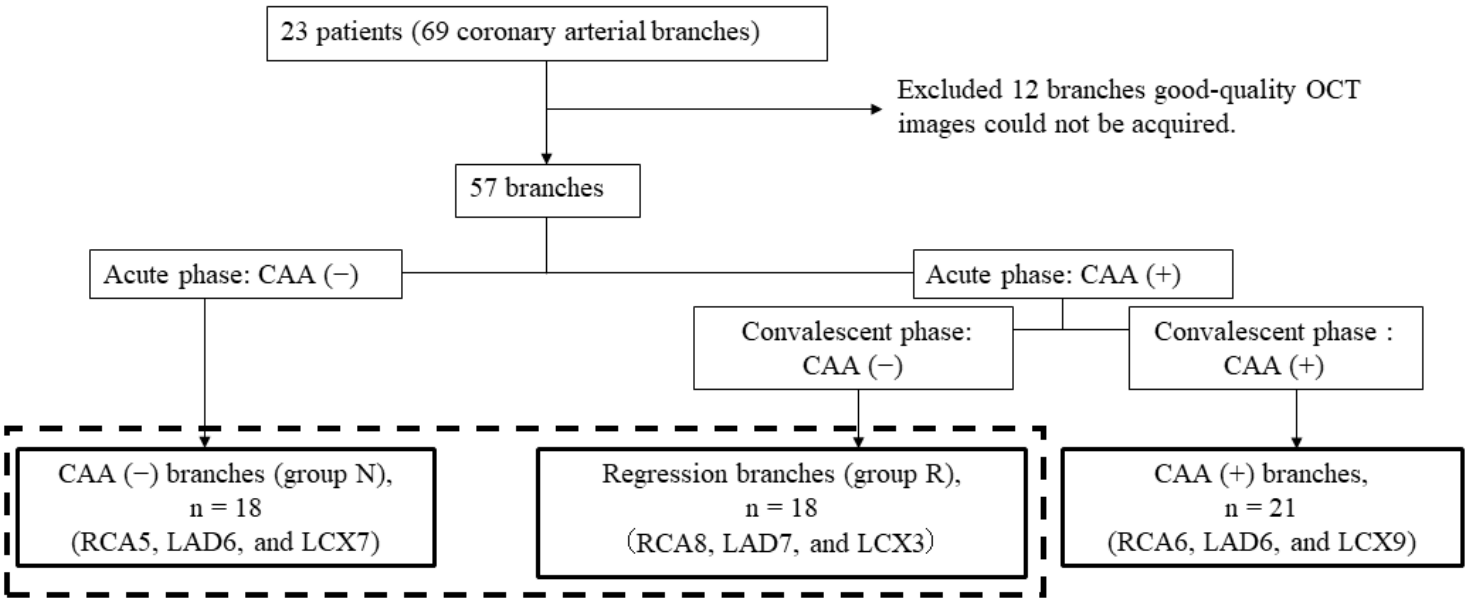

Figure 2

Study flowchart. KD, Kawasaki disease; CAG, coronary angiography; OCT, optical coherence tomography; CAA, coronary artery aneurysm; RCA, right coronary artery; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery.

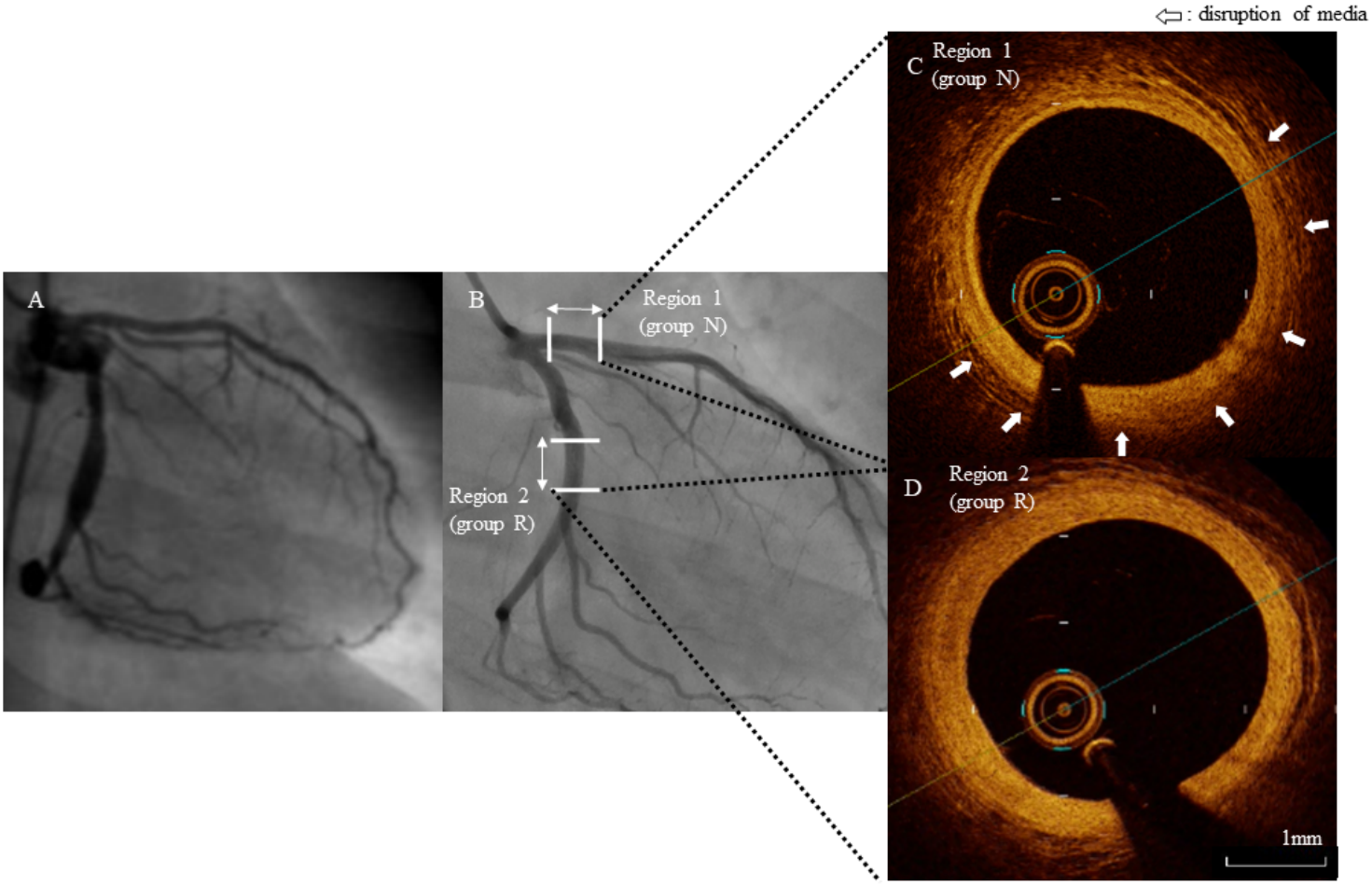

Figure 3

A and B: left coronary angiography in the same patient at 2 time points (A, age 9 months, acute phase 53 days after onset; B, age 12 years and 10 months, convalescent phase 12 years and 2 months after onset). C and D: optical coherence tomography (OCT) images of a coronary artery in the convalescent phase (C, Region 1; D, Region 2). (A) The left anterior descending coronary artery (LAD) appears normal (proximal inner diameter, 2.1 mm) and the left circumflex artery (LCX) has a small coronary artery aneurysm (CAA) (maximum inner diameter, 4.0 mm). (B) The LAD is still normal (proximal inner diameter, 3.1 mm; region 1; classified in group N) and the LCX CAA has regressed (inner diameter, 2.7 mm; region 2; classified in group R). (C) OCT of region 1 shows the three arterial lamina, partial disruption of the media (white arrows), and mild intimal thickening. (D) OCT of region 2 shows widespread abnormal intimal thickening and disruption of the media.