

Pathological Features of Coronary Arteries in Children With Kawasaki Disease in Which Coronary Arterial Aneurysm Was Absent at Autopsy

Quantitative Analysis

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Coronary arteries in six children who had Kawasaki disease but lacked coronary arterial aneurysms were examined. Four children died of myocarditis at the acute stage, and two children died of bacterial sepsis or as a result of an occurrence during cineangiography at the healed stage. Twenty-one children without Kawasaki disease were examined as controls. The six children with Kawasaki disease had no thrombi, recanalization, or stenosis greater than 50% in the major coronary arteries. Three patients had dilatation of the major coronary arteries at the acute stage. Two of the three patients died during the acute stage, and autopsy showed slight dilatation of coronary arteries and abnormal intimal thickening due to panvasculitis. In the third child, who died at the healed stage, dilatation of the coronary arteries detected by two-dimensional echocardiography at the acute stage had disappeared at the healed stage. No dilatation of the major coronary arteries was seen at autopsy. However, abnormal fibrous intimal thickening of the major coronary arteries without inflammatory changes was found. The other three patients had no dilatation of the major coronary arteries at the acute stage. Two patients died at the acute stage, and slight inflammation without abnormal intimal thickening was seen in the intima and the adventitial area. In the third patient, who died during the healed stage, two-dimensional echocardiography revealed no dilatation during the clinical course, and there was no inflammatory changes or abnormal intimal thickening at autopsy. We conclude that in Kawasaki disease, vasculitis of the major coronary arteries is present even in patients without coronary dilatation at the acute stage, and the abnormal intimal thickening may or may not remain at the healed stage. Kawasaki disease without coronary aneurysm has the same pathological entity as Kawasaki disease with coronary aneurysm. (*Circulation* 1988;78:345–350)

In patients with Kawasaki disease, the frequency of coronary arterial aneurysms is approximately 20%.¹ According to previous autopsy studies,^{2–7} the coronary arteries show acute angitis in the acute stage, and scar tissue forms with marked intimal thickening in the healed stage. In patients with Kawasaki disease, the mortality was 0.3–0.4%,¹ and almost all of the patients who died had coronary aneurysms of 6 mm or greater in

diameter.⁷ Therefore, whether a coronary arterial lesion can develop in Kawasaki disease without coronary arterial aneurysms has not been reported. We studied the histological features of coronary arteries in patients with Kawasaki disease without coronary arterial aneurysms.

Patients and Methods

Patients

The patients were six Japanese children with Kawasaki disease in whom coronary arterial aneurysm was not noted at autopsy. Nakano et al⁸ defined coronary arteries 4 mm or greater in diameter as coronary aneurysm clinically.⁸ In the present study, a coronary artery without aneurysm was defined as a coronary artery with elastic interna less than 4 mm in diameter. Dilatation of coronary artery was defined as the elastic interna with a

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Supported in part by a research grant from the Ministry of Health and Welfare, Tokyo, Japan.

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Received December 8, 1987; revision accepted April 14, 1988.

diameter between the upper limit of the control and 4 mm. There were five boys and one girl between the ages of 3 months and 4 years and 7 months. All children had typical clinical signs and symptoms of Kawasaki disease in the acute stage.

As controls, 21 autopsied children without Kawasaki disease (12 boys and nine girls; aged 2 months to 4 years) were studied.

Methods

After fixation with 10% formalin, the three major coronary arteries were sectioned transversely at 2–3-mm intervals in their entirety from the ostia to periphery and were observed macroscopically. Then, all of the sections were embedded in paraffin and cut at 4- μ m thickness by a microtome. They were stained with hematoxylin and eosin, elastic van Gieson's stain, and Masson-trichrome. The specimens stained with elastic van Gieson were magnified at $\times 60$ –160, and the coronary arteries were traced on white paper for quantitative analysis.⁷ Thickness of intima, circumferences of the cavity (L1) and elastic interna (L2) of the coronary arteries, and length of destruction of the elastic interna (D) were measured with an image analyzer. Diameter of the coronary arterial cavity was calculated from circumference of the cavity ($2r=L1/\pi$) to exclude factors of artificial deformity. Diameter of the elastic interna was also calculated from the circumference of the elastic interna ($2r=L2/\pi$). Percent destruction of the elastic interna was calculated with the equation $100 \times D/L2$.

Stages of patients with Kawasaki disease were classified as stages 1–4 according to the duration of illness from the onset to death^{2,6,7}: stage 1, within 9 days of illness; stage 2, 12–25 days of illness; stage 3, 28–32 days of illness; and stage 4, over 40 days of illness. Acute stage was defined as stages 1–3, and healed stage was defined as stage 4.

Results

In 12 control patients between 2 and 11 months old, the mean \pm SD of maximal diameter of the coronary arterial cavity and maximal diameter of the elastic interna were 1.0 ± 0.4 mm (maximum, 1.8 mm) and 1.1 ± 0.4 mm (maximum, 1.9 mm), respectively. Maximal destruction of the elastic interna was $18 \pm 22\%$ (maximum, 81%). Fibrous thickening of the intima was also seen partially or in the whole circumference, and maximal thickness of the intima of each specimen was 92 ± 60 μ m (maximum, 225 μ m) (Figure 1A). In nine control patients between 1 and 4 years old, maximal diameter of the coronary arterial cavity and maximal diameter of the elastic interna were 1.2 ± 0.3 mm (maximum, 2.0 mm) and 1.4 ± 0.3 mm (maximum, 2.4 mm), respectively. Maximal destruction of the elastic interna was $28 \pm 23\%$ (maximum, 82%). Fibrous thickening of the intima was seen, and maximal thickness of intima of each specimen was 150 ± 72 μ m (maximum, 290 μ m) (Figure 1B).

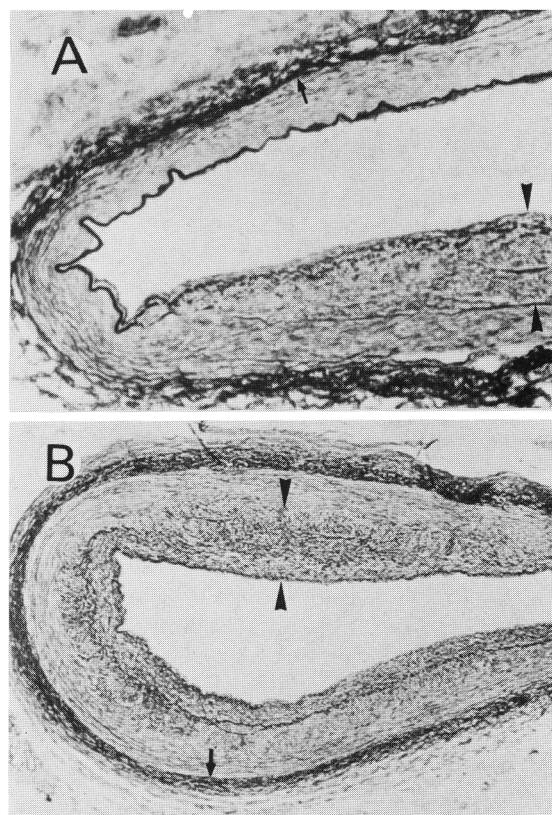


FIGURE 1. Photomicrographs of coronary arteries in two children without Kawasaki disease. Panel A: Patient was a 10-month-old girl. Destruction of elastic interna was 19%. Maximal thickness of intima was 148 μ m. Diameter of elastic interna was 1.4 mm (original magnification, $\times 40$; elastic van Gieson's stain). Panel B: Patient was a 3-year-old boy. Destruction of elastic interna was 43%. Maximal thickness of intima was 193 μ m. Diameter of elastic interna was 1.5 mm (original magnification, $\times 25$; elastic van Gieson's stain). Arrowheads, elastic interna and endothelium at intima with maximal thickness; arrows, elastic externa.

Table 1 summarizes the results of the study of six children with Kawasaki disease. Macroscopically, there was no thrombi, stenosis greater than 50%, or recanalization noted in the coronary arteries in these patients. Patients 1–4, who died during the acute stage (stages 1–3), showed acute myocarditis at autopsy. Two of these four patients died suddenly, and the other two died of heart failure. In patient 1, who died on the 9th day of illness, acute inflammation was noted in the intimal and adventitial areas and was rare in the media. Inflammatory tissue was edematous and was infiltrated chiefly with neutrophils, eosinophils, and lymphocytes, some of which were atypical. Maximal destruction of the elastic interna, maximal thickness of the intima, and maximal diameter of the major coronary artery (cavity and elastic interna) were within normal limits. Patients 2 and 3 died at 18 (3-month-old boy) and 19 days of illness (1-year-old boy) with

TABLE 1. Quantitative Analysis of Coronary Arteries in Children With Kawasaki Disease Lacking Coronary Arterial Aneurysms

	Patient					
	1	2	3	4	5	6
Clinical stage	Stage 1	Stage 2			Stage 4	
Duration of illness	9 days	18 days	19 days	22 days	46 days	2 years, 2 months
Sex	Male	Male	Male	Female	Male	Male
Age at death	10 months	3 months	1 year	3 months	11 months	4 years, 7 months
Cause of death	MC*	MC†	MC*	MC†	Sepsis	AMI
Maximal diameter of arterial cavity (mm)	1.7	2.2‡	2.1‡	1.2	1.5	1.6
Maximal diameter of elastic interna (mm)	1.8	2.6‡	2.5‡	1.3	1.7	2.4
Acute inflammation of coronary artery						
Intima	+	+++	+++	+	—	—
Media	—	+++	+++	—	—	—
Adventitia	+	+++	+++	+	—	—
Perivascular area	+++	+++	+++	+	—	—
Destruction of elastic interna (%)	5	84	69	7	27	68
Maximal thickness of intima (μm)	45	300‡	345‡	70	110	800‡

Degree of inflammation of coronary artery was classified from + (Figure 2B) to +++ (Figure 2A). — Indicates no acute inflammatory change.

MC, myocarditis; Sepsis, sepsis due to *Staphylococcus aureus*; AMI, acute myocardial infarction due to spasms induced during cineangiography.

*Sudden death; †heart failure; ‡over upper limits of control.

severe panvasculitis and severe inflammation of the perivascular area (Figure 2A). Infiltrating cells included neutrophils, eosinophils, lymphocytes, atypical lymphocytes, plasma cells, monocytes, fibroblasts, and fibrocytes. Slight dilatation of the major coronary artery was seen where panvasculitis was noted. In these two patients, maximal intimal thickness was abnormal. Maximal destruction of elastic interna was within the upper limit of controls. Patient 4 was a 3-month-old girl who died on the 22nd day of illness without any dilatation or aneurysm detected by two-dimensional echocardiography during her clinical course. Microscopically, slight mononuclear cell infiltration in the coronary arteries was localized in the intima and adventitial areas (Figure 2B). Maximal destruction of the elastic interna, maximal thickness of intima, and maximal diameter of the major coronary artery were within normal limits.

Patients 5 and 6 died during the healed stage of Kawasaki disease (stage 4). Patient 5 was a 10-month-old boy who developed a fever and rash 30 days after the onset of Kawasaki disease (i.e., after the acute signs and symptoms of Kawasaki disease had disappeared). Culture of blood revealed *Staphylococcus aureus*. He died of complicated pneumonia on the 46th day after the onset of Kawasaki disease. There was no dilatation or aneurysm of coronary arteries as determined by serial two-dimensional echocardiography during his clinical course. Microscopic examination of coronary arteries revealed no inflammatory cell infiltration (Figure

3A). Maximal destruction of the elastic interna, maximal thickness of intima, and maximal diameter of the major coronary artery were within normal limits.

Patient 6 was 2 years and 5 months old when he developed Kawasaki disease. With two-dimensional echocardiography, dilatation of coronary arteries was noted during the acute stage but disappeared after 1 year. Although the patient was well until he was 4 years and 7 months old, marked spasm of the left anterior descending coronary artery followed by acute myocardial infarction occurred during cineangiography. He died 2 days after the onset of spasm. Microscopic examination revealed no inflammatory cell infiltration in the coronary arteries (Figure 3B). Maximal destruction of the elastic interna and maximal diameter of the coronary arterial cavity were within normal limits. Maximal diameter of elastic interna was at the upper limit of controls. However, abnormal and fibrous intimal thickening of coronary artery of 800 μm was detected. In addition, autopsy revealed acute antero-septal myocardial infarction.

Discussion

We previously reported that lesions of the major coronary arteries in patients with Kawasaki disease change dynamically with time: acute inflammatory changes are seen in the intima and the adventitial area in stage 1 (within 9 days), and inflammation progresses into the media and becomes panvascular in stage 2 (12–25 days). Subsequently, coronary

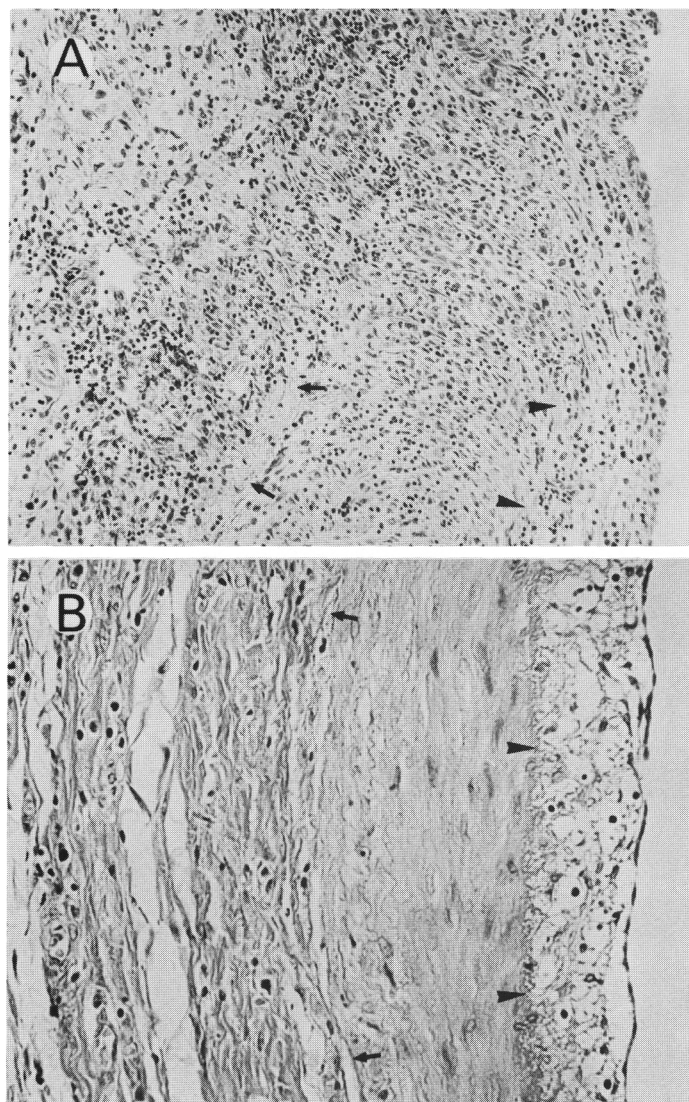


FIGURE 2. Photomicrograph of coronary arteries of patients with Kawasaki disease without aneurysm at acute stage. Panel A: Histology of major coronary artery with dilatation. Note presence of severe panvasculitis and perivascular inflammation. Inflammatory tissue was edematous and infiltrated chiefly with neutrophils, eosinophils, lymphocytes, atypical lymphocytes, plasma cells, monocytes, fibroblasts, and fibrocytes. Photograph was obtained from patient 2 (original magnification, $\times 100$; hematoxylin and eosin stain). Panel B: Histology of major coronary artery without dilatation. Slight inflammatory changes are seen in intima and adventitial area. Note infiltrate of slight mononuclear cell infiltration. Photograph was obtained from patient 4 (original magnification, $\times 200$; hematoxylin and eosin stain). Arrowheads, elastic interna; arrows, elastic externa.

aneurysms with thrombi appear. Granulation tissue is observed in stage 3 (28–32 days), and scar formation consisting of marked fibrous intimal thickening, recanalization, thrombi, or severe stenosis emerge in stage 4 (more than 40 days). These characteristics were obtained from the autopsied children with coronary aneurysm, and coronary arterial lesion of Kawasaki disease was defined as acute vasculitis.²

The present study revealed that the six children without coronary aneurysm did not have macroscopic thrombi, severe stenosis, or recanalization. They died of myocarditis at the acute stage or a bacterial sepsis or an accident at the healed stage. This finding supports our hypothesis⁷ that only children with coronary aneurysm die of coronary heart disease as sequela of Kawasaki disease.

Even in babies without cardiac disease,^{9–11} the destruction of the elastic interna and intimal thickening have been reported in the coronary arteries. Eighty percent destruction of the elastic interna was

noted in our controls. Hence, the destruction we observed in the elastic interna in patients with Kawasaki disease without aneurysm was within the upper limits. However, in three patients with dilatation of the major coronary arteries during the acute stage, intimal thickening over the upper limits of controls was seen due to panvasculitis at the acute stage and fibrous thickening at the healed stage. In the three patients lacking coronary dilatation at the acute stage, inflammation of coronary arteries was slight during the acute stage and disappeared without abnormal intimal thickening during the healed stage. These findings suggest that dilatation or lack of dilatation depends on the severity of the inflammation in the major coronary arteries; the healing process for each situation is different. Probably, the abnormal fibrous intimal thickening is involved in the regression of coronary arterial dilatation as seen in patient 6. However, the following discrepancy is noted between pathology of the coronary arteries and clinical data: clinical signs

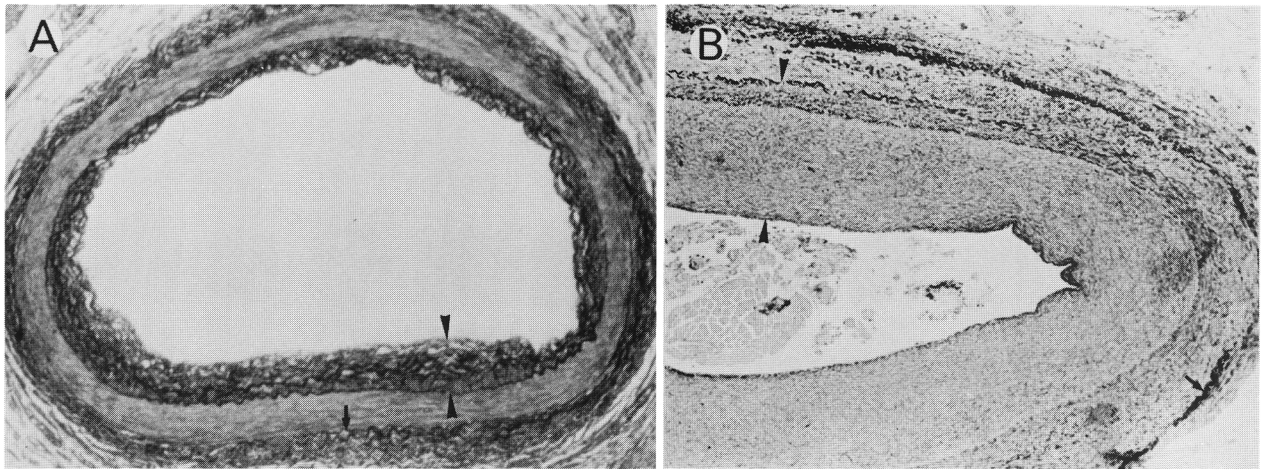


FIGURE 3. Photomicrographs of coronary arteries of patients with Kawasaki disease lacking aneurysm during healed stage. Panel A: Histology of major coronary artery in patient 5 who had no dilatation at acute and healed stages. Diameter of arterial cavity and elastic interna was 1.5 and 1.7 mm, respectively. Destruction of elastic interna and maximum thickness of intima was 16% and 110 μ m; these were within normal limits (original magnification, $\times 40$; elastic van Gieson's stain). Panel B: Histology of major coronary artery in patient 6 in which dilatation revealed by two-dimensional echocardiography at acute stage regressed at healed stage. Note diffuse abnormal thickening of intima (450 μ m). However, destruction of elastic interna was within normal limits. Diameter of arterial cavity and elastic interna was 1.6 and 2.4 mm, respectively (original magnification, $\times 20$; elastic van Gieson's stain). Arrowheads, intima; arrows, elastic externa.

(e.g., C-reactive protein, platelet count, and white blood cell count) in patients who died, regardless of the size of coronary arteries, were severe and similar to those of surviving patients with coronary aneurysm¹²; in surviving patients without coronary aneurysm, clinical data were mild,¹³ and the distinction between patients with dilatation and without dilatation was impossible.¹² This discrepancy suggests that clinical signs in patients with Kawasaki disease reflect not only vasculitis of the coronary arteries but also inflammation in the whole body. Thus, it is indicated that Kawasaki disease without coronary aneurysm has the same pathological entity as Kawasaki disease with coronary aneurysm. However, because the number of patients in the present study was small, we cannot deny the possibility that some of the many surviving patients without coronary aneurysm have no vasculitis of the major coronary arteries at the acute stage.

We conclude that in patients with Kawasaki disease, angitis of the major coronary artery is present even in patients without coronary dilatation at the acute stage. In such patients, abnormal intimal thickening may or may not remain at the healed stage.

Acknowledgments

We thank Satoko Tomita, Keiko Ishikawa, and Naomi Araki for their technical assistance and Tomoko Takenami and Michie Jinnai for expert secretarial assistance. We are also indebted to Daniel Mrozek for preparation of the manuscript. We wish to express our appreciation to Dr. David T. Purtilo

for his thoughtful review of our manuscript and to Dr. Yoshihiro Hamashima for pertinent discussion.

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KEY WORDS • absence of coronary arterial aneurysm •
two-dimensional echocardiography • Kawasaki disease •
coronary arterial lesion