Active Remodeling of the Coronary Arterial Lesions in the Late Phase of Kawasaki Disease
Immunohistochemical Study
Atsuko Suzuki, MD; Sachiko Miyagawa-Tomita, PhD; Keiko Komatsu, BA; Toshio Nishikawa, MD; Yasunari Sakomura, MD; Toshinobu Horie, MD; Makoto Nakazawa, MD

Background—Remodeling of the coronary artery lesions in Kawasaki disease has been observed in longitudinal angiographic studies. However, mechanisms of such remodeling have not yet been elucidated.

Methods and Results—We examined formalin-fixed specimens of the coronary arteries immunohistochemically by using antibodies against vascular growth factors (GFs) and their receptors in 7 children with Kawasaki disease, 9 children with no coronary disease, and 3 adults with atherosclerosis. In the thickened intima at stenotic sites and at recanalized vessels with Kawasaki disease, extensive expression of vascular GFs, such as transforming GF-β1, platelet-derived GF-A, and basic fibroblast GF, was observed both within and surrounding smooth muscle cells. Vascular endothelial GF was observed within smooth muscle cells. Furthermore, all of these GFs were strongly expressed in the newly formed microvessels within the intima. In the thinned media, these GFs were focally and weakly expressed. In contrast, these GFs were expressed only in the media in the control children. In cases of adult atherosclerosis, GFs were expressed diffusely in the media but focally and weakly if at all in the intima.

Conclusions—Active remodeling of the coronary artery lesions in Kawasaki disease continues in the form of luxuriant intimal proliferation and neoangiogenesis for several years after the onset of the disease. This process is distinct from adult-onset atherosclerosis. (Circulation. 2000;101:2935-2941.)

Key Words: growth substances ▪ vasculature ▪ stenosis ▪ aneurysm ▪ thrombosis

Progressive localized stenosis and remarkable development of recanalized vessels in the occluded aneurysm are often observed by angiographic follow-up study in the late phase of Kawasaki disease,1–3 and the progressive stenotic lesions often cause sudden death even years after the onset. The basic mechanisms of such vascular remodeling have not been studied. A number of studies on coronary atherosclerosis in adult patients have been performed with the use of immunohistochemical techniques in fresh-frozen specimens of the vessels.4 In Kawasaki disease, however, it is virtually impossible to obtain such fresh samples because patients usually die suddenly outside the hospital. Besides, there is no animal model of Kawasaki disease. Recently, however, it has been shown that immunohistochemical study is feasible in formalin-fixed specimens.5 Accordingly, we undertook the present study to examine the contribution of various growth factors (GFs) in the progression of intimal thickening in the late phase of Kawasaki disease by using specimens that had been preserved in formalin for a long time.

Clinical Profile
We examined 7 cases of Kawasaki disease (Table 1); the age at onset ranged from 6 months to 3 years, and the year of onset ranged from 1974 to 1985. As to acute-phase treatment, steroids, aspirin, and/or dipyridamole were used in 4 patients and treatment was unknown in 3 patients. In the late phase, all patients had been given anticoagulants. Coronary artery surgery was performed in 4 patients. Myocardial infarction occurred in 6 patients 12 days to 8 months after onset, excluding 1 case of unknown time after onset, and 5 patients showed no subjective symptoms. Angina began in 3 patients >3 years after onset. Six patients died suddenly of acute myocardial infarction and another of ischemic heart failure at 2 to 12 years after onset. On autopsy, localized stenosis was seen in 6 patients at the inlet and/or outlet of aneurysms of the left coronary arteries. The aneurysms, associated with localized stenosis, were occluded by a fresh thrombus in 3 patients. All the organized thrombotic occlusions had recanalized vessels.2

Tissue Specimens
The specimens of Kawasaki disease had been preserved in formalin solution for 11 months to 18 years. The specimens include 5 segments of localized stenosis, 11 aneurysms, and 5 segments of old thrombotic occlusion with subsequent recanalization (Table 1).
TABLE 1. Tissue Specimens of Kawasaki Disease

<table>
<thead>
<tr>
<th>Age at Onset</th>
<th>Death</th>
<th>Treatment (Acute)</th>
<th>Angina</th>
<th>SMI (Q)</th>
<th>Surgery, Age</th>
<th>Anticoagulants (Late Phase)</th>
<th>Cause of Death</th>
<th>Preserved</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6 mo</td>
<td>5 y</td>
<td>Unknown</td>
<td>Angina at 4 y</td>
<td>ACB: 4 y 7 mo</td>
<td>Aspirin, warfarin, dipyridamole</td>
<td>AN, LS*</td>
<td>AN</td>
</tr>
<tr>
<td>2</td>
<td>6 mo</td>
<td>5 y 7 mo</td>
<td>Steroid, aspirin</td>
<td>SMI (Q) at 53 d and 2.1 y; HF at 4 y 6 mo</td>
<td>...</td>
<td>Aspirin, dipyridamole</td>
<td>AN AN*, LS AN* OC</td>
<td>AMI 15 y</td>
</tr>
<tr>
<td>3</td>
<td>1 y 4 mo</td>
<td>6 y 9 mo</td>
<td>Unknown</td>
<td>SMI at unknown age; angina at 5 y 11 mo</td>
<td>ACB: 6 y 6 mo</td>
<td>Warfarin, dipyridamole, ticlopidine</td>
<td>AN*, LS AN*, LS (fTh)</td>
<td>OC OC*</td>
</tr>
<tr>
<td>4</td>
<td>3 y 9 mo</td>
<td>7 y 1 mo</td>
<td>Steroid, aspirin</td>
<td>SMI (Q) at 8 mo; angina at 6 y</td>
<td>Angioplasty; 7 y 1 mo</td>
<td>Aspirin</td>
<td>LS* AN* AN*, LS</td>
<td>OC*</td>
</tr>
<tr>
<td>5</td>
<td>1 y 6 mo</td>
<td>4 y 2 mo</td>
<td>Aspirin, dipyridamole</td>
<td>SMI (Q) at 12 d</td>
<td>...</td>
<td>Aspirin, dipyridamole</td>
<td>AN* AN*, LS* AN*, LS (fTh)</td>
<td>OC*</td>
</tr>
<tr>
<td>6</td>
<td>3 y 3 mo</td>
<td>15 y 6 mo</td>
<td>Unknown</td>
<td>AMI at 26 d and 1.5 mo; HF at 12 y 3 mo</td>
<td>ACB: 6 y 6 mo</td>
<td>Warfarin</td>
<td>AN* OC OC* OC</td>
<td>HF</td>
</tr>
<tr>
<td>7</td>
<td>3 y 6 y 9 mo</td>
<td>Steroid</td>
<td>SMI (Q) at 4 mo</td>
<td>...</td>
<td></td>
<td>Aspirin, ticlopidine, dipyridamole</td>
<td>... AN*, LS (fTh)</td>
<td>OC OC*</td>
</tr>
</tbody>
</table>

SMI indicates silent myocardial infarction; (Q), appearance of abnormal Q waves; AMI, acute myocardial infarction with subjective symptom; HF, heart failure; ACB, aortocoronary bypass surgery; LMT, left main trunk; LAD, left anterior descending coronary artery; LCx, left circumflex artery; RCA, right coronary artery; AN, aneurysm; LS, localized stenosis; OC, occlusion with recanalized vessels; and fTh, fresh thrombus.

*Examined lesion.

We also studied specimens for a normal control from 9 children who had had no coronary artery disease (Table 2). Specimens from 3 of them had been preserved in formalin for 11 to 20 years, and those from another 4 were fixed in formalin for 1 night. The remaining 2 were fresh-frozen specimens. We used them not only for the normal control study but also to compare the patterns of staining between fresh samples and old formalin-preserved samples. To compare the remodeling pathology, we studied 3 adult patients who had had no coronary artery disease (Table 2). Specimens from those from another 4 were fixed in formalin for 1 night. The remaining 2 were fresh-frozen specimens. We used them not only for the normal control study but also to compare the patterns of staining between fresh samples and old formalin-preserved samples.

All coronary arteries were dehydrated and embedded in paraffin. We also studied specimens for a normal control from 9 children who had had no coronary artery disease. Specimens from 3 of them had been preserved in formalin for 11 to 20 years, and those from another 4 were fixed in formalin for 1 night. The remaining 2 were fresh-frozen specimens. We used them not only for the normal control study but also to compare the patterns of staining between fresh samples and old formalin-preserved samples. To compare the remodeling pathology, we studied 3 adult patients who had had no coronary artery disease. Specimens from those from another 4 were fixed in formalin for 1 night. The remaining 2 were fresh-frozen specimens. We used them not only for the normal control study but also to compare the patterns of staining between fresh samples and old formalin-preserved samples.

All coronary arteries were dehydrated and embedded in paraffin.

Serial sections (6 μm) were stained with hematoxylin-eosin, Victoria blue–van Gieson, and Masson-trichrome stains. Immunohistochemical staining was performed 3 times for each region for all antibodies, and 2 to 3 serial sections were used each time for each factor to confirm the specific pattern of staining.

To determine interobserver variability, 3 of us (A.S., S.T., Y.S.) examined each staining. Only the findings reached by consensus were adopted as positive or negative data. As to the evaluation of the degree of expression, “strong” expression was defined as deeply stained cells in high-power magnification or densely concentrated positive cells in lower-power magnification. “Weak” expression was defined as a faintly stained positive cell or sparsely distributed positive cells among the same cell group. Further, we classified the expression as diffuse and focal.

Antibodies Tested

The antibodies used were against transforming GF-β1 (TGF-β1), TGF-β type I receptor (TβRI-I), platelet-derived GF-A (PDGF-A), basic fibroblast GF (bFGF), vascular endothelial GF (VEGF) (Santa Cruz Biotech), TGF-β type II receptor (TβRII) (Upstate Biotech), and α-actin for identification of smooth muscle cells and macrophages (Dako).

Immunohistochemistry

Except for α-actin and TGF-β1 antigens, antigen retrieval was performed with trypsin, pepsin (Zymed), or hyaluronidase (Sigma) or by boiling in citric acid monohydrate.

Tissues for frozen sections were fixed in 4% paraformaldehyde for 20 minutes. They were transferred to 5% to 30% sucrose in PBS before embedding in OCT compound and frozen. Frozen sections (10 μm) did not require antigen retrieval.

The sections were treated with 5 mmol/L periodic acid for 10 minutes. They were then preincubated with PBS containing 0.5%
skim milk, 3% goat serum, and 0.1% sodium azide (blocking solution) for 15 minutes at 37°C. The following primary antibodies were subsequently diluted in the blocking solution or PBS containing 1% BSA and 0.1% sodium azide: TGF-β1 (1:25), TβR-I (1:800), TβR-II (1:20), PDGF-A (1:40), VEGF (1:100), bFGF (1:100), α-actin (1A4, 1:50), and macrophages (CD68, 1:20; HAM56, 1:20). After incubation with the primary antibodies for 2 to 3 days at 4°C, the sections were washed in PBS containing 0.5% skim milk. Immunoreactivities were detected with an ABC kit (Vector Labs). Peroxidase activity was visualized by 0.02% 3-3′ diaminobenzidine (Sigma) and 0.05% hydrogen peroxide. The sections were counterstained with hematoxylin. Two different controls were used. Negative controls were incubated with normal nonimmune sera instead of the primary antibodies. Second, each antibody was preincubated with the appropriate antigen (Santa Cruz Biotech) before the immunohistochemical staining was performed. No immunoreactivity was seen in either of these controls.

Results
Normal Coronary Artery
In the normal coronary artery, both TβR-I and TβR-II (Figure 1, A-I and A-II) were expressed diffusely and similarly in the medial smooth muscle cells but not detected in the intima. The amount of TβR-I-positive cells is approximately same as the amount of TβR-II-positive cells. This pattern of expression was the same as that observed with bFGF (Figure 2A) TGF-β1, PDGF-A, VEGF, and α-actin (data not shown).

When we compared the expression pattern of these GFs and receptors between the freshly fixed specimens and those fixed for a lengthy period, we noticed that the expression pattern was identical, except that the staining tended to be a little weaker against the background in the formalin-preserved specimens.

Coronary Artery Lesions of Kawasaki Disease
Localized Stenosis
At the localized stenosis, there were multiple layers within markedly thickened intima, consisting of linearly arranged microvessels, layers rich in smooth muscle cells, and fibrous layers. The lamina interna was disrupted at many points, with a large number of medial smooth muscle cells migrating into the intima (Figure 3A). Abundant stellate-shaped smooth muscle cells were observed at the cell-rich layer in the middle intima, indicating their active proliferation (Figure 3B). The media layer was very thin, whereas the adventitia was thick, interspersed with numerous vasa vasorum. There was no accumulation of lipid or macrophages in the intima. TβR-I and TβR-II were expressed diffusely in the thick intima, but they were expressed only focally in the media. The intimal TβR-II-positive cells (Figure 1, B-II) were apparently fewer compared with the intimal TβR-I-positive cells (Figure 1, B-I). The positive cells were identified as smooth muscle cells by the presence of actin, which was observed in serial sections.

The expression of bFGF (Figure 2B and Figure 3I), TGF-β1 (Figure 3C), and PDGF-A (Figure 3D) were basically similar in distribution to that of TβRs, and they were expressed principally within the smooth muscle cells but also expressed extracellularly. TGF-β1 (Figure 3E), PDGF-A, VEGF (Figure 3F), and bFGF (Figure 2B and Figure 3I) were also expressed strongly in microvascular smooth muscle cells. VEGF (Figure 4E) and bFGF (Figure 2B) were expressed especially strongly in the adventitial vasa vasorum.

VEGF was expressed in the intimal smooth muscle cells and more strongly expressed in the endothelial cells of the neomicroves-
sels in the intima (Figure 3F). In the layer of deep intima adjacent to the media, the VEGF-positive cell groups were connected to adventitial vasa vasorum by tiny tubes through the media (Figure 3G). Some macrophages, which were stained by antimacrophage antibody, were observed around these angiogenic sites (Figure 3H).

**Aneurysm**

None of the aneurysms observed in this study with the exception of one contained either endothelial cells or cell-rich layers, and advanced scar tissue and calcifications filled the aneurysmal wall; thus, no staining of GFs could be clearly observed. In one aneurysm there was a cell-rich layer in the innermost part of the intima expressing GFs focally and sparsely.

**Occlusion**

Organized thrombotic occlusion contained well-developed recanalized vessels, which were surrounded by a thick smooth muscle cell layer where α-actin was strongly expressed (Figure 4B). The thick smooth muscle cell layer was further surrounded by a line of numerous microvessels (Figure 4A). The intima of the occluded native aneurysm was not thick but was often difficult to distinguish from the adjacent thick smooth muscle cell layer of recanalized vessels. The media of occluded aneurysm was thin and severely degenerated where α-actin was sparsely expressed (Figure 4B). The adventitia had abundant vasa vasorum, and some of them were observed to be connected with new recanalized vessels (Figure 4E).

TGF-β1, PDGF-A, and bFGF were diffusely and strongly expressed in the thick smooth muscle cell layers of the newly recanalized vessels (Figure 4, C, D, and F). These GFs were only focally expressed in severely degenerated media of occluded aneurysms and not at all expressed in the organized thrombus. VEGF was expressed strongly in the endothelial cells and in the perivascular smooth muscle cells of neomicrovessels in the thrombus and vasa vasorum (Figure 4E). bFGF was also expressed strongly in the vasa vasorum and smooth muscle cells of neomicrovessels (Figure 4F).

**Atherosclerosis**

Advanced atherosclerosis showed fibrous layers, a mass of cholesterol crystals, and accumulation of a large number of macrophages at the plaque shoulder lesions in the intima, but the media and adventitia were apparently normal (Figure 1, C-I and C-II). TβR-I and TβR-II were expressed approximately in the same degree in the media but in the intima TβR-II–positive smooth muscle cells (Fig 1, C-II) appeared somewhat less than TβR-I–positive cells (Figure 1, C-I). The expression of TGF-β1 and PDGF-A were focal and weak in the smooth muscle cells of media and intima, and their distributions were similar to that of TβRs. bFGF (Figure 2C) and VEGF were expressed diffusely in the medial smooth muscle cells but not in the intima, unlike the intima of Kawasaki disease. All the data are summarized in Table 3.

**Discussion**

In the present study, we found that the coronary arterial lesions in Kawasaki disease are still undergoing active remodeling many years after the onset of the disease. This process appears to be different from that occurring in atherosclerosis in adult patients. Progressive localized stenosis in Kawasaki disease consists of remarkable intimal thickening caused by proliferative dense smooth muscle cells and accumulation of fibrous tissue. The lamina interna was disrupted at many points where the medial smooth muscle cells appear to migrate into the intima. In addition, the intimal smooth muscle cells were stellate-shaped, indicating that these cells were actively proliferating. These smooth muscle cell–rich areas strongly and diffusely coexpressed TGF-β1, PDGF-A, and bFGF, both intracellularly and extracellularly. Currently, we do not know the factors that trigger mRNA expressions for these GFs. On the other hand, in the intima of atherosclerosis, these GFs were expressed very weakly or not at all. Besides, unlike atherosclerosis, there were neither fatty streaks nor accumulation of macrophages in Kawasaki disease specimens.

These results are compatible with the notion that TGF-β1 stimulates proliferation of smooth muscle cells by PDGF-A and bFGF.
as well as synthesis of extracellular matrix by smooth muscle cells. Recently, McCaffrey et al have reported that the migration and proliferation of smooth muscle cells in response to TGF-β occurs in the injured vessels. Injured smooth muscle cells are induced to proliferate markedly and to excrete large quantities of extracellular matrix. McCaffrey et al. have also shown that this process is associated with a decreased ratio of type II/type I TGF-β receptors. It was intriguing that the ratio of type II/type I receptor–positive cells in the intima were very likely decreased in Kawasaki disease.

TGF-β is known to be preserved in its inactive form and is converted to a biologically active form in several situations, such as the stimulation of endothelial cells by platelet aggregation, exposure to steady shear stress, or the presence of mild pH change and/or plasmin. In Kawasaki disease, it is highly possible that the platelets aggregate in the aneurysm as the result of turbulent flow, thus activating latent TGF-β. Furthermore, shear stress is increased at the inlet and outlet of the aneurysm, where almost all progressing localized stenosis with intimal thickening appeared.

Exposure of the endothelium to increased shear stress induces the expression of tissue plasminogen activator, which then converts the latent TGF-β to the activated form and provides a mechanism for the release of biologically active bFGF from the extracellular matrix. bFGF has been reported to be a strong inducer of smooth muscle cell synthesis together with PDGF-AA homodimer. In our study, bFGF was expressed together with PDGF-A in the thick intima of Kawasaki disease. PDGF-A may be possibly expressed as PDGF-AA homodimer or as PDGF-AB heterodimer. PDGF-AA together with bFGF may stimulate active synthesis of smooth muscle cells in the intima.

Another possibility of cause of intimal proliferation is an increase in angiotensinogen production, which induces the PDGF-A. However, we have no information about the in situ activation of angiotensin II in the context of late-phase Kawasaki disease, and up to now we have not been able to quantify angiotensinogen mRNA expression in our formalin-fixed specimens.
Aneurysm regression occurs usually within several months after the disease. Thereafter, the size of aneurysm either does not change or decreases slowly only in some cases. This clinical observation can be explained by the result of the present study. In most of our aneurysm specimens, the aneurysm wall was totally replaced by thick fibrous scar tissue and had no remaining endothelial cells or a cell-rich layer that would normally express GFs, indicating that no active remodeling was taking place within the aneurysm proper. Tissue expressing GFs was observed only in 1 of 11 aneurysm specimens and may have been progressive intimal thickening.

As to neoangiogenesis, which is another important feature of vascular remodeling in Kawasaki disease, it is reported that VEGF is expressed in the medial smooth muscle cells of normal coronary artery at a low level and that the strong expression of VEGF at the vascular wall is an evidence of active angiogenesis. In our study, overexpression of VEGF was observed at well-developed recanalized vessels in the occluded aneurysms, microvessels in the thick intima, and numerous vasa vasorum in the adventitia. Additionally, strong expression of TGF-β, PDGF-A, and bFGF in the neovascular smooth muscle cells and the appearance of macrophages around new vessels indicate active angiogenesis even in the late phase.

Finally, the present study has obvious limitations because immunohistochemistry was done with specimens preserved in formalin for long periods. We first carried out a careful absorption test for each GF and receptor and examined fresh specimens to compare the pattern of staining with that of the old specimens. On the basis of these studies, we found that the methodology we used was acceptable. However, we were not able to carry out accurate quantitative analysis by these immunohistochemical methods. To elucidate the precise role of the GFs in the time sequence of coronary artery remodeling in Kawasaki disease, one must quantify mRNA expression at various stages of the disease. Such studies were impossible with our formalin-preserved specimens.

In conclusion, in Kawasaki disease, the arterial lesions continue to undergo active remodeling processes several years after the onset of the disease. These processes are different from that of adult-type atherosclerosis. Better understanding of the basic mechanisms of long-term coronary arterial remodeling may lead us to more effective and innovative treatments for patients with Kawasaki disease.

Acknowledgments

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### Table 3. Atherosclerosis

<table>
<thead>
<tr>
<th>Layer</th>
<th>TßR-I, -II</th>
<th>TGF-ß,</th>
<th>PDGF-A</th>
<th>VEGF</th>
<th>bFGF</th>
<th>α-Actin</th>
<th>Macrophage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localized stenosis (5 lesions)</td>
<td>Intima</td>
<td>Inner</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td>Middle</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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</tr>
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<td></td>
<td>Deep</td>
<td>+</td>
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<td>+</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Adventitia</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
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<tr>
<td>Aneurysms (11 lesions)</td>
<td>Intima</td>
<td>Inner</td>
<td>−§</td>
<td>−§</td>
<td>−§</td>
<td>−§</td>
<td>−§</td>
</tr>
<tr>
<td></td>
<td>Middle</td>
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<tr>
<td></td>
<td>Deep</td>
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<td>+</td>
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<td>+</td>
<td>+</td>
<td>−§</td>
</tr>
<tr>
<td></td>
<td>Media</td>
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<td>+</td>
<td>+</td>
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</tr>
<tr>
<td></td>
<td>Adventitia</td>
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<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Occlusion (5 lesions)</td>
<td>Organized thrombus</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td></td>
<td>Artery within artery</td>
<td>+§</td>
<td>+§</td>
<td>+§</td>
<td>+§</td>
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<tr>
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<td>Media</td>
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<tr>
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</tr>
<tr>
<td>Control</td>
<td>Intima</td>
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<tr>
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<td>Adventitia</td>
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<td>−</td>
<td>−</td>
<td>−</td>
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<tr>
<td>Children, normal artery (18 sites)</td>
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<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
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<tr>
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<tr>
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<td>Adventitia</td>
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<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Atherosclerosis (6 lesions)</td>
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<td>−</td>
<td>−</td>
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<td>−</td>
<td>−</td>
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<tr>
<td></td>
<td>Adventitia</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>−</td>
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</table>

Expression (−) is indicated as no growth factor; +, focal; *, diffuse; †, concentrated in wall of microvessels; §, localized to areas surrounding microvessels; only 1 of 11 specimens contained layer rich in smooth muscle cells.

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