Original Article

The pathology of Kawasaki disease aortitis: a study of 37 cases ☆,☆☆

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A B S T R A C T

Background: Kawasaki disease (KD) is a systemic vasculitis syndrome that occurs most frequently in children. Most clinical and pathological studies have focused on its coronary artery lesions. To date, no detailed studies of the aorta have been conducted. We studied KD autopsy cases with the aims of clarifying the time-course of changes in aortic lesions, the differences in the inflammatory cells and degree of inflammation at various aortic sites, and the progression of the inflammation.

Materials and Methods: The study materials were aortic specimens taken from 37 KD autopsy cases (acute phase: 19; remote phase: 18). Twenty-seven of the cases also had coronary aneurysms. We chose 3 aortic sites, i.e., the thoracic aorta, aortic root and aortic bifurcation, and we histologically observed and compared those sites in regard to the changes with time, the kinds of infiltrating cells and the number of inflammatory cells. We also observed the relationship between the vasa vasorum and inflammatory cell localization in the tunica media, and examined the progression of inflammation in the tunica media.

Results: Destruction of the vascular architecture was not seen in any of the 37 cases, but inflammatory cell infiltration was observed in 90% of the acute-phase cases. The inflammatory cell infiltration involved the tunica intima and tunica adventitia of the aorta on the 6th disease-day, and all layers of the aorta on the 13th disease-day; the infiltration peaked on the 18th disease-day. The infiltration gradually disappeared thereafter, and no significant infiltration was seen in the remote phase. The infiltrating inflammatory cells consisted mainly of CD163-positive macrophages. Comparison of the 3 sites of the aorta showed that the inflammatory cell infiltration was more severe in the aortic root and aortic bifurcation than in the thoracic aorta. The progression of inflammation to the aortic tunica media from the adventitia showed 2 patterns: 1 in which macrophages were aggregated around the vasa vasorum; and a second in which there was no such aggregation around the vasa vasorum, but there was diffuse inflammatory cell infiltration of the tunica media. In addition to this, there were findings of direct infiltration of cells from the tunica intima into the tunica media.

Conclusion: Inflammation in KD occurs in the aorta. The changes with time and the kinds of infiltrating cells were the same as reported to date for coronary arteries in KD. There were differences in the degree of inflammation among the 3 aortic sites. It can be thought that the inflammation from the adventitia to the media progresses via the vas vasorum, and also, there is a possibility of spreading directly. From the intima to the media, inflammation spreads directly. However, formation of aneurysms and destruction of the vascular architecture of the aorta were absent in this study, unlike in coronary arteries.

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1. Introduction

Kawasaki disease (KD) was first reported by Dr. Tomisaku Kawasaki in 1967. KD is an acute febrile exanthematous illness that occurs most frequently in children, and for which the cause is still unknown [1,2]. KD is classified as a systemic vasculitis syndrome. The medium-sized muscular arteries, especially the coronary arteries, are the most frequently involved. Histopathological reports on the coronary arteries indicate that inflammation of the arteries begins around the 6th day of the disease and becomes panvasculitis by about the 10th day. By about the 12th day, as a result of inflammation of all layers and circumferential arteritis, the severely damaged arteries begin to dilate and form aneurysms. The severe inflammation continues for 2 weeks, followed by gradual healing of the scars. Formation of coronary artery aneurysms,

Table 1
Antibodies that were used

	Antibody to	Clone	Type	Source
CD163	Macrophages	10D6	Monoclonal	Leica Biosystems
CD66	Neutrophils*	BY114	Monoclonal	BIOGENEX LABORATORY
CD3	T lymphocytes		Polyclonal	Dako
CD20	B lymphocytes	L26	Monoclonal	Dako
CD34	Vascular endothelial cells	QBEnd 10	Monoclonal	Dako
Von Willebrand Factor	Vascular endothelial cells	F8/86	Monoclonal	Dako

* Neutrophils were defined as CD66-positive segmented leukocytes.

with thrombotic occlusion, was reported in a majority of autopsy cases [3,4].

Clinical and pathological studies of KD to date have focused on coronary artery lesions because ischemic heart disease caused by thrombotic occlusion of aneurysms secondary to vasculitis is directly linked to the cause of death. However, it is known that vasculitis also develops in other arteries throughout the body [5].

There have been no pathological reports of detailed studies that focused on the large arteries in KD. For that reason, we carried out the present histopathological study in which we investigated the presence and degree of inflammation in various sites of the aorta, as well as the details of the infiltrating cells. Our aims were to clarify the time-course of changes in aortic lesions and the differences in inflammation in the various sites. We also investigated the involvement of the vasa vasorum in the progression of acute aortic inflammation.

2. Materials

The subjects consisted of aortic specimens from 37 autopsy patients with KD. The study controls were autopsy specimens from 3 non-KD children.

This study was approved by the Ethics Committee of Toho University Ohashi Medical Center (Approval No.: H16080).

3. Methods

Aortic specimens were selected that corresponded to the following 3 sites: (1) thoracic aorta (thoracic descending aorta with no nearby bifurcations), (2) aortic root (thoracic ascending aorta, 1 cm above a coronary artery bifurcation), and (3) aortic bifurcation (1 cm on the proximal side of a thoracic descending aorta from the intercostal artery bifurcation.).

The following cases were studied: the thoracic aorta in 17 acute-phase cases and 18 remote-phase cases; the aortic root in 10 acute-phase cases and 6 remote-phase cases; and the aortic bifurcation in 4 acute-phase cases and 4 remote-phase cases.

3.1. Histological evaluation of the aortic wall

The aortic sections were formalin-fixed, paraffin-embedded, thin-slices. We prepared 1 paraffin block per site, with 1 fragment per block. They were stained with hematoxylin and eosin (H&E), as well as elastica van Gieson (EvG) stain. The stained thin-slices were observed for the extent of intimal thickening and the presence of infiltrating cells; degeneration of smooth muscle cells; and rupture of elastic fibers in the tunica media. Next, to classify the types and numbers of the inflammatory cells more accurately, immunohistochemical techniques were used to identify macrophages, neutrophils, T cells, and B cells. Table 1 shows the antibodies that were used. Neutrophils were defined as CD66-positive segmented leukocytes. For all of the formalin-fixed, paraffin-embedded thin-slices, antigens were retrieved using DTLink (Dako Co.; CA, USA), followed by staining using an automated immunohistochemistry stainer (Agilent Technology Ltd.; CA, USA).

The immunostained aortic specimens were divided into 4 regions: tunica intima, inner half of the media, outer half of the media, and tunica adventitia. Five points in each region were randomly selected, and high-magnification (x400) tissue photographs were taken using a microscope camera (DP20; Olympus, Tokyo, Japan). Then, after counting the numbers of macrophages, neutrophils, T cells, and B cells in the photographs, the numbers were corrected to per 100 μm $\times$ 100 μm. The average value of the 5 points was used as the number of infiltrating cells in each region. Data were expressed as the mean $\pm$ SD for the 5 points.

1) Time-course changes in the infiltrating cells in each aortic site

The total numbers of macrophages, neutrophils, T cells, and B cells in each region, i.e., tunica intima, inner half of the media, outer half of the media, and tunica adventitia, were added up to obtain the total number of inflammatory cells. We then examined for relationships between the disease-day and the total inflammatory cell counts in the thoracic aorta, the aortic root and the aortic bifurcation.

2) Time-course changes and types of inflammatory cells in each region of the thoracic aorta

We examined the numbers of infiltrating macrophages, neutrophils, T cells, and B cells in the 4 regions, i.e., tunica intima, inner half of the media, outer half of the media, and adventitia of the specimens from the 35 thoracic aorta cases. We also examined the changes in those cell counts with time.

3) Comparison of the infiltrating cells in each of the thoracic aorta, aortic root, and aortic bifurcation

In addition, for 8 cases for which the thoracic aorta and the aortic root were able to be compared in the same case, and for 4 cases in which the aortic bifurcation and the thoracic aorta could be compared, we analyzed the inflammatory cell counts in each region of the thoracic aorta, aortic root and aortic bifurcation. Quantitative analyses were performed using the Mann-Whitney U test (Statflex; Artec Co., Ltd.; Osaka, Japan). P values of <.01 were considered to indicate statistical significance.

4) Examination of the control specimens

The same examinations as above were performed for the control specimens, and the findings were compared with those for the KD cases.

3.2. Investigation of the vasa vasorum in the thoracic aorta

We observed the morphology and course of the vasa vasorum in the thoracic aorta specimens from 12 acute-phase cases on the 6th to the 30th disease-days. In addition to H&E and EvG staining, anti-CD34 antibody and anti-von Willebrand factor antibody were used to identify vascular endothelial cells in the vasa vasorum, and anti-CD163 antibody was used to identify macrophages (Table 1). The immunostaining methods were the same as described above. Moreover, we prepared 400 serial sections of a block from a patient who had died on the 18th disease-day and which showed

the most severe inflammation in all layers of the aorta. We then observed the course of the vasa vasorum and examined the relationship between the vasa vasorum and the localization of inflammatory cell infiltration in the aortic wall.

4. Results

4.1. Histological evaluation of the aortic wall

1) Time-course changes in the infiltrating cells in each aortic site

The details of the 37 subjects are shown in Table 2. As 3 control cases, the ages at death were 2, 4, and 9 years, and the M:F sex ratio was 1:2. The causes of death were one case each of primary pulmonary hypertension, acute encephalopathy and influenza-associated encephalopathy. Observation of the H&E–and EvG–stained sections showed that the basic structure of the aorta was maintained in all of the 19 acute-phase cases, and there was no rupture of tunica media elastic fibers, degeneration of smooth muscle cells, necrosis, dissection, etc. Moreover, no thrombi were observed.

The time-course changes in the inflammatory cells were as follows. The degree of inflammatory cell infiltration in each site increased with time, peaked out around the 18th day, and decreased thereafter (Fig. 1). However, slight differences existed between the sites. In the aortic root, the same level of strong cell infiltration was still seen even on the 23rd, 27th, and 30th days (Fig. 1b). Aortic bifurcation was observed in only 4 cases, on the 10th, 16th, 23rd, and 28th disease-days, but the largest number of inflammatory cells was seen in a patient who died on the 23rd disease-day (Fig. 1c).

In remote-phase patients who died after the 40th disease-day, intimal thickening was mild in each of the thoracic aorta, aortic root, and aortic bifurcation. Moreover, there were no findings indicative of loss of smooth muscle cells or elastic fiber rupture in the tunica media, or fibrosis of the tunica adventitia. In the immunohistological examinations, only very small numbers of cells were positive for the various antibodies, and they were almost the same as or slightly higher than the numbers seen in the control cases.

2) Time-course changes and types of inflammatory cells in each region of the thoracic aorta

We investigated the inflammatory cells infiltrating each of the thoracic aorta regions of the 35 KD autopsy specimens. The largest total number of inflammatory cells was seen in the tunica intima, followed by the tunica adventitia, the outer half of the media and the inner half of the media (Fig. 2). In the tunica intima and adventitia, inflammatory cell infiltration was seen on the 6th day. Infiltration was seen in the outer half of the media on the 10th day, and in the inner half of the media on the 13th day. In every region, the infiltration peaked on the 18th day and then gradually decreased.

In each of the thoracic aorta regions and throughout the time-course, CD163-positive macrophages were by far the most predominant infiltrating inflammatory cells (Fig. 2, Fig. 3). A few CD3-positive T lymphocytes and a very small number of CD66-positive segmented neutrophils were also present. CD66-positive neutrophils were few in number in each of the regions. A few CD3-positive T lymphocytes were also seen in each region, except for in the inner half of the media. CD20-positive B lymphocytes were very small in number and seen only in the outer half of the media and the tunica adventitia.

3) Comparison of the infiltrating cells in each of thoracic aorta, aortic root, and aortic bifurcation

For 8 KD cases, the numbers of inflammatory cells in the aortic root and thoracic aorta of the same case were able to be compared. In 4 of those cases (cases 3, 10, 11, and 13), the total number of inflammatory cells in the arterial wall was greater in the aortic root than in the thoracic aorta (Fig. 4). The inflammatory cell infiltration in each region was examined in the aortic root and thoracic aorta. Many inflammatory cells had infiltrated the tunica intima and tunica adventitia, and they were continuous with the nearby coronary arteritis (Fig. 5a–c).

In 4 cases, the aortic bifurcation and thoracic aorta were able to be compared. In 3 of those cases, the inflammatory cell infiltration was more severe in the aortic bifurcation (Fig. 6). Comparing the regions of the aortic bifurcation, many inflammatory cells had infiltrated the tunica intima and tunica adventitia, and they were continuous with the arteritis in the nearby bifurcated arteries (Fig. 5d–f).

4.2. Investigation of the vasa vasorum in the thoracic aorta

In all 12 examined cases, the vasa vasorum was present from the tunica adventitia to the outer half of the media, but it could not be confirmed in the inner half of the media or in the tunica intima. The course of the vasa vasorum was confirmed in serial section specimens from the 18th disease-day. The vasa vasorum entered from the tunica adventitia, extended toward the inner lumen while branching or anastomosing, and then bent and coursed horizontally in the outer third of the media. However, the vasa vasorum was confined to the outer half of the media, and it was not seen to extend to the tunica intima side.

With regard to the relationship between the localization of inflammatory cells and the vasa vasorum, there were instances in which macrophages were aggregated around the vasa vasorum and instances in which macrophages were diffusely distributed, without any aggregation (Fig. 7). In the former instance, macrophage infiltration around the vasa vasorum was striking in 2 cases on the 10th disease-day, and mild in 3 cases on, respectively, the 13th, 18th, and 30th disease-days. There were no findings of rupture of aortic elastic fibers or degeneration of smooth muscle cells, etc., around the vasa vasorum. Mild swelling of vasa vasorum endothelial cells was observed in 2 cases on the 10th disease-day, but there were no findings of vasa vasorum luminal occlusion. On the other hand, in the latter instance, direct inflammatory cell infiltration from the tunica adventitia to the tunica media was seen on the 24th disease-day and in 4 cases on the 27th–30th disease-days. About the inner half of the media, inflammatory cells were observed to infiltrate directly from the tunica intima (Fig. 7b).

5. Discussion

In this study, inflammatory cell infiltration was confirmed in the aortic wall in 90% of acute-phase KD deaths. Histopathological examinations conducted to date found frequencies of inflammatory cell infiltration of the aorta ranging from 41% to 82% [5–8]. The main reported histological findings were mild endoarteritis [7], endoarteritis with intimal fibrosis, and mild inflammatory cell infiltration along the vasa vasorum in the tunica media [8]. Our present study is the first to find that inflammatory cells had spread to all layers of the aorta.

No previous reports examined the time-course of changes in inflammation of the aorta or the details of the infiltrating cells. In the aorta, we first saw inflammatory cell infiltration of the tunica intima and tunica adventitia on the 6th disease-day. In the 13th disease-day case, inflammatory cell infiltration of the tunica media had progressed, leading to full-thickness inflammation. The inflammatory cell infiltration peaked at around the 18th disease-day, and

Table 2
Clinical information

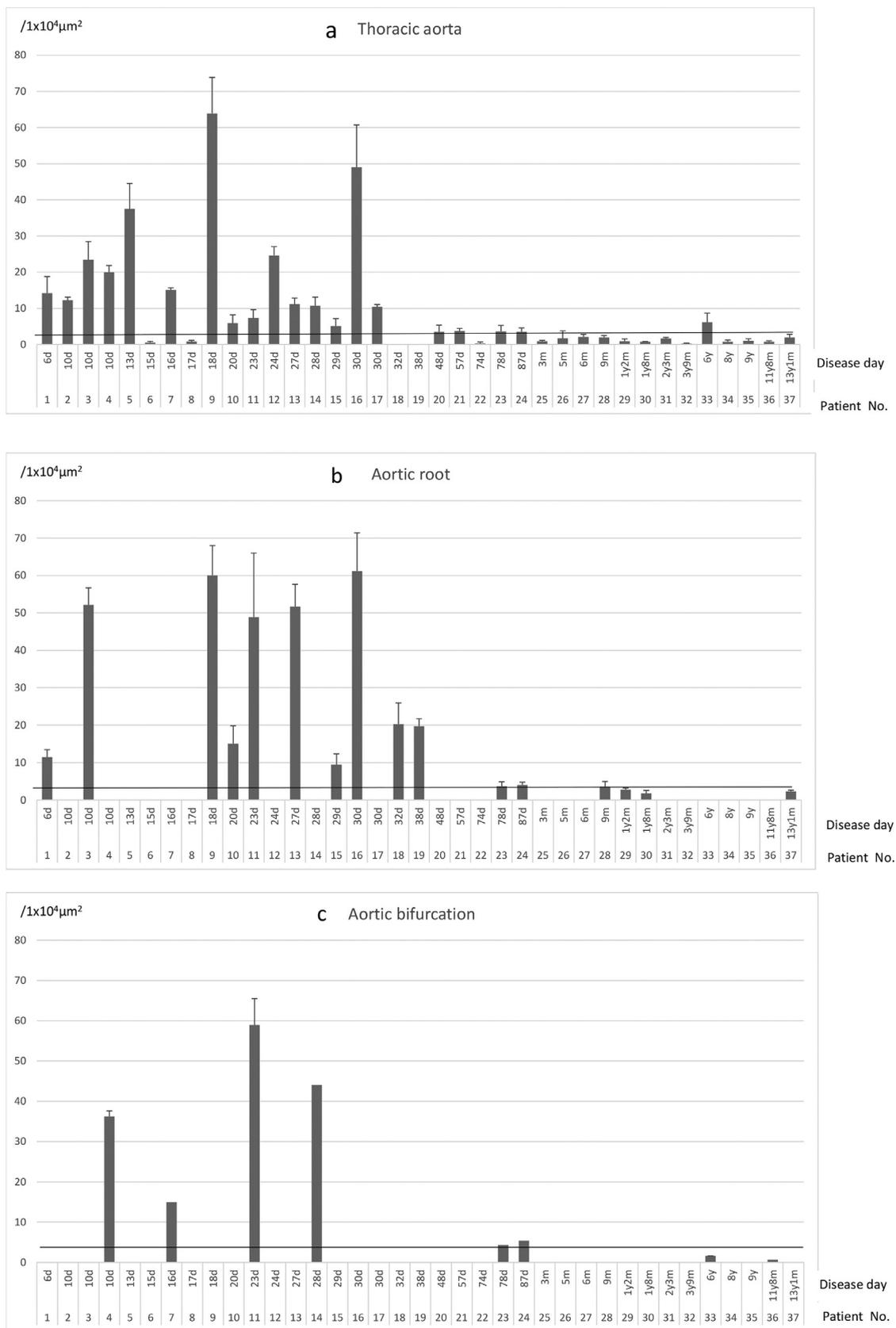| Patient No.	Age	Gender	Disease day	Thoracic aorta				Coronary artery		Aortic root				Intercostal artery		Aortic bifurcation				Notes
				tunica intima	inner half of the media	outer half of the media	tunica adventitia	Inflammation	Aneurysm	tunica intima	inner half of the media	outer half of the media	tunica adventitia	Inflammation	Aneurysm	tunica intima	inner half of the media	outer half of the media	tunica adventitia	
1	05y02m	M	6d	+	−	−	+	+	−	+	−	+	+							
2	06y00m	M	10d	+	−	+	+	+	−											Died of fungal sepsis while being treated for leukemia
3	03y00m	M	10d	+	−	−	+	+	−	+	−	+	+							
4	04y00m	M	10d	+	−	+	+	+	+					+	−	+	−	−	+	Rupture of coronary aneurysm
5	00y09m	F	13d	+	+	+	+	+	−											
6	00y03m	F	15d	−	−	−	−	+	+											
7	00y02m	M	16d	+	−	+	+	+	+					+	−	+	−	−	+	
8	01y05m	M	17d	−	−	−	−	+	+											Rupture of coronary aneurysm
9	00y11m	M	18d	+	+	+	+	+	+	+	−	+	+							Died of myocardial infarction
10	01y10m	M	20d	+	−	−	+	+	−	+	−	−	+							
11	00y03m	F	23d	−	−	+	+	+	+	+	+	+	+	+	−	+	+	+	+	
12	00y04m	M	24d	+	+	+	+	+	+											Rupture of coronary aneurysm
13	00y03m	M	27d	+	+	+	+	+	+	+	+	+	+							
14	00y04m	M	28d	+	−	+	+	+	+					+	+	+	−	−	+	
15	01y07m	F	29d	+	−	−	+	+	−	+	−	+	+							Died of interstitial pneumonia
16	00y07m	M	30d	+	+	+	+	+	+	+	−	+	+							
17	00y03m	F	30d	+	+	+	+	+	+											
18	00y02m	M	32d					+	+	+	+	+	+							
19	00y04m	M	38d					+	+	+	+	+	+							
20	00y11m	M	48d	−	−	−	+	+	+											
21	01y06m	M	57d	−	−	−	−	+	+											
22	04y00m	F	74d	−	−	−	−	−	−											Died of bronchopneumonia
23	00y05m	M	78d	−	+	+	−	+	+	−	−	+	+	−	−	+	−	−	−	
24	02y06m	M	87d	+	−	−	−	−	+	−	−	+	+	−	−	+	−	−	−	Sudden death
25	00y08m	F	3m	−	−	−	−	−	+											
26	00y08m	F	5m	−	−	−	−	−	+											
27	02y00m	F	6m	−	−	−	−	−	+											
28	02y00m	F	9m	−	−	−	−	+	−	−	−	−	−							Died of meningitis
29	02y02m	M	1y2m	−	−	−	−	−	−	+	−	−	−							Sudden death
30	05y00m	M	1y8m	−	−	−	−	−	+	−	−	−	−							
31	04y11m	M	2y3m	−	−	−	−	−	+											
32	04y00m	M	3y9m	+	−	−	−	−	+											
33	09y00m	M	6y	−	−	−	−	−	+							−	−	−	−	
34	09y00m	M	8y	−	−	−	−	−	+											
35	12y00m	F	9y	−	−	−	−	−	+											Died 3 y 1 mo after bypass surgery
36	12y00m	M	11y8m	−	−	−	−	−	−							−	−	−	−	Sudden death
37	17y00m	M	13y1m	−	−	−	−	−	+	−	−	−	−							Sudden death

4

Fig. 1. Time-course changes in the number of infiltrating inflammatory cells at each site. Line: the average value of the 3 control cases.
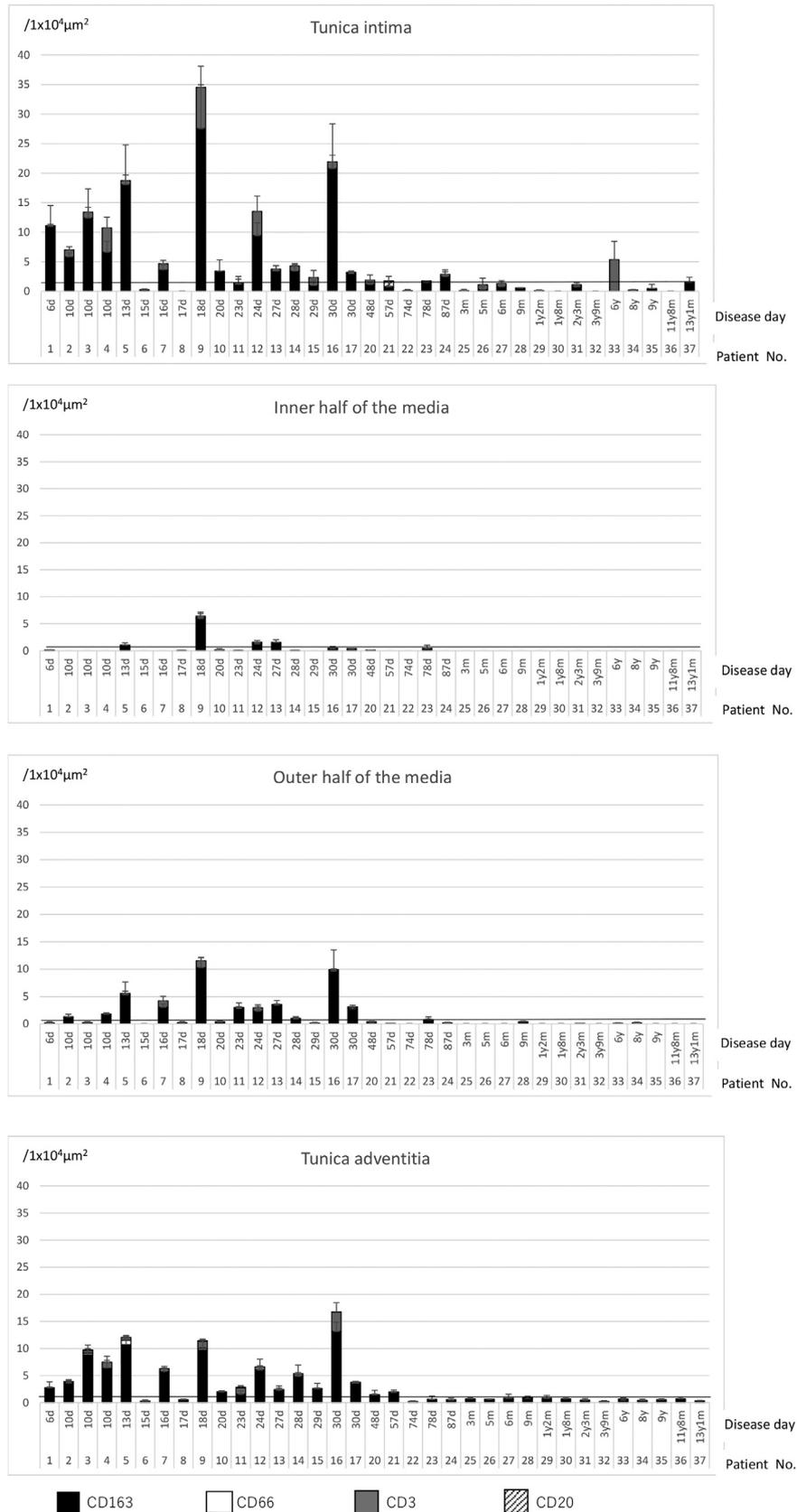
Fig. 2. Changes in the number of inflammatory cells in each thoracic aorta region, and the types of infiltrating inflammatory cells. Line: the average value of the 3 control cases.
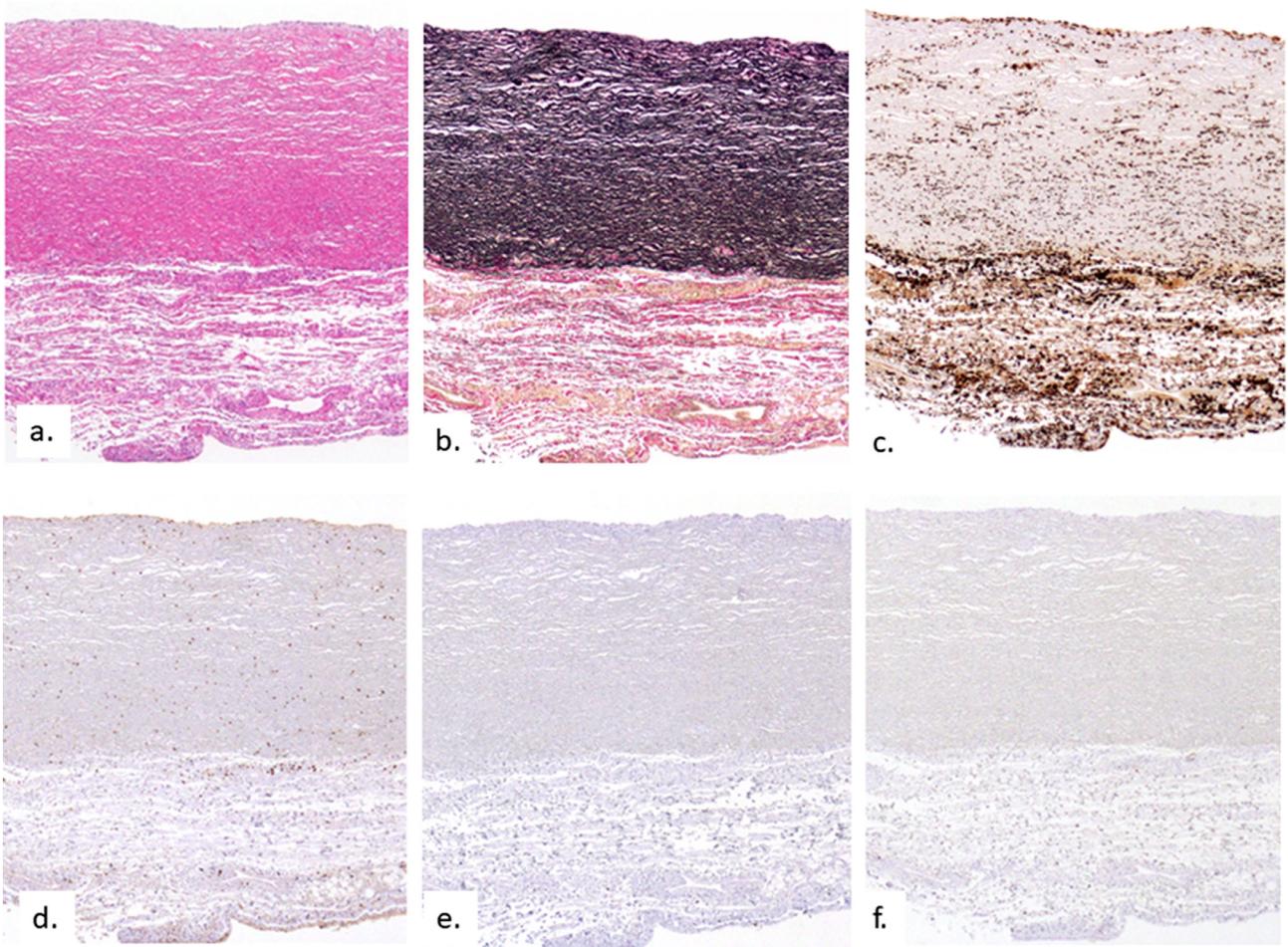
Fig. 3. Light microscopic findings for the aorta of Case 9, 18th day of illness. (a) H&E staining. Inflammatory cell infiltration is unclear. (b) EvG staining. No rupture of elastic fibers is seen. The vascular architecture is preserved. (c) CD163. The main infiltrating cells are CD163-positive macrophages. (d) CD3. A small number of CD3-positive T lymphocytes is mixed in. (e) CD66. A small number of CD66-positive neutrophils is seen in the tunica adventitia, but almost none in the tunica media. (f) CD20. No CD20-positive B lymphocytes were seen in most cases.
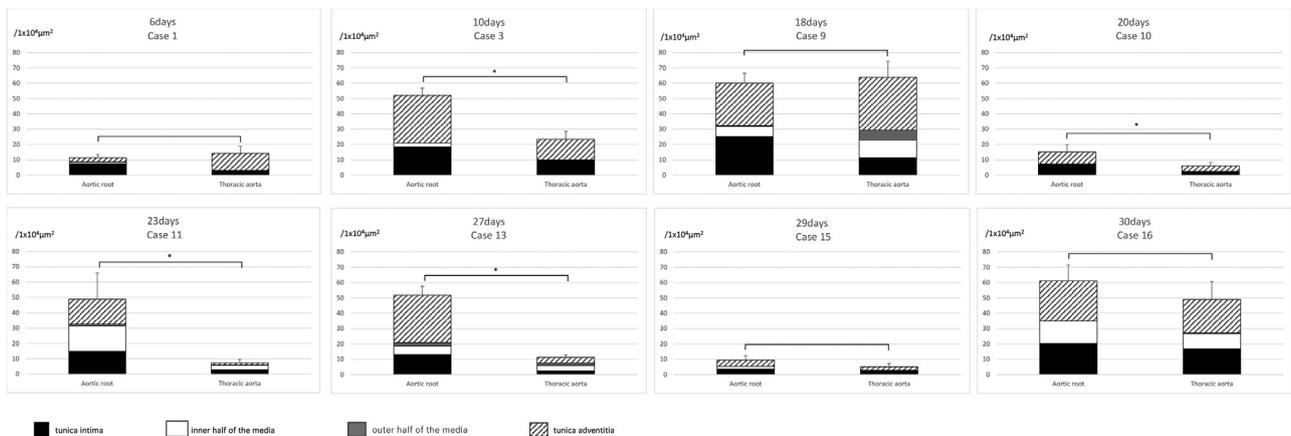
Fig. 4. Comparison between aortic root and thoracic aorta (total number of inflammatory cells in each region). Comparing the aortic root with the thoracic aorta, 4 out of 8 cases showed a high degree of inflammatory cell infiltration of the aortic root, especially in the tunica adventitia. * $P<.01$.

disappeared in the remote phase. The infiltrating cells were predominantly macrophages, but there were also small numbers of T lymphocytes and neutrophils. These time-course changes in the inflammatory cell infiltration of the aorta and the details of the infiltrating cells are consistent with those reported for histological studies of coronary artery lesions [9–11]. It is thus clear that aortic inflammation develops in synchrony with coronary arteritis and

follows a monophasic course of progression. However, our present examination of autopsy cases found coronary aneurysms in 27 of the 37 cases, but no aortic aneurysms or rupture of tunica media elastic fibers. With regard to aortic aneurysms, we found only 9 case reports that dealt with aortic aneurysms [12–20]. Furthermore, Hoshino et al. [21] reported formation of abdominal aortic aneurysms in 7 of 17 cases who had systemic artery aneurysms. On
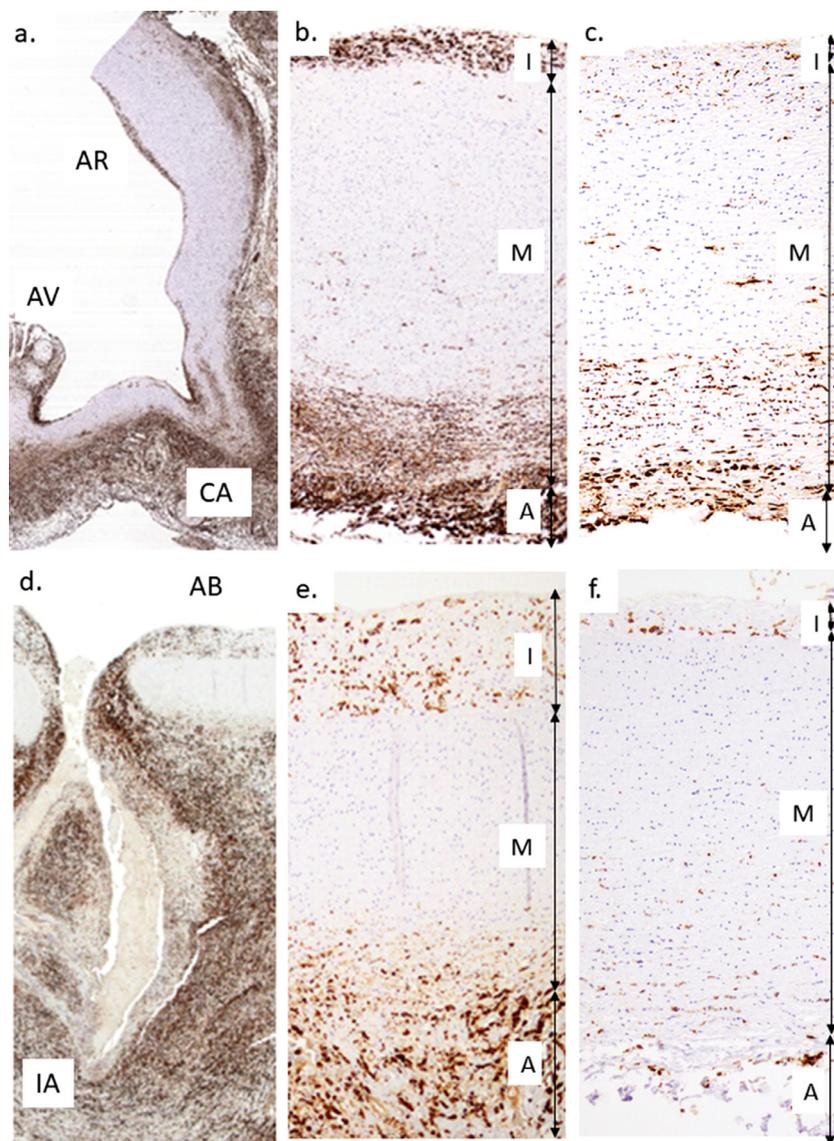
Fig. 5. Comparisons of the aortic root and thoracic aorta, and of the aortic bifurcation and thoracic aorta. CD163-positive macrophages. Case 16, 30th disease-day. (a) aortic root; (b) aortic root; (c) thoracic aorta. Inflammatory cell infiltration was continuous from the coronary arteries to the aortic root via the tunica intima and tunica adventitia. Many CD163-positive macrophages are seen in the aortic root compared with the thoracic aorta. Case 14, 28th disease-day. (d) Aortic bifurcation; (e) aortic bifurcation; (f) thoracic aorta. Inflammatory cell infiltration was continuous from the bifurcated muscular artery to the aortic bifurcation via the tunica intima and tunica adventitia. Many CD163-positive macrophages are seen in the aortic bifurcation compared with the thoracic aorta. AR: aortic root; AV: aortic valve; CA: coronary artery; AB: aortic bifurcation; IA: intercostal artery; I: intima; M: media; A: adventitia.

the other hand, Ichinose et al. [22] reported that, out of 616 children with KD who had a coronary artery aneurysm, 19 also had an aneurysm in another artery, only one of which was an aneurysm of the abdominal aorta. Thus, it can be thought that formation of an aortic aneurysm in KD is extremely rare. The reason for the difference in the frequency of aneurysms even though inflammation was observed in more than 90% of both coronary arteries and aortas may be that the inflammation of the coronary arteries was severe enough to destroy the vascular architecture, whereas inflammation of the aorta was mild and it can be thought that destruction of the wall structure is rare. In cases with aortic aneurysm formation, it may be that inflammation equivalent to that of the coronary arteries also developed in the aorta.

We compared the degree of inflammation in each part of the aorta in the same cases. We found that the inflammation was more severe in the aortic root and aortic bifurcation than in the thoracic aorta; it was especially severe in the tunica intima and tunica adventitia. The aortic root and aortic bifurcation showed inflamma-

tion of the nearby medium-sized muscular arteries, such as the coronary and intercostal arteries, and it is speculated that inflammation of these bifurcated arteries spreads directly to the tunica intima and tunica adventitia of the aorta. The total number of inflammatory cells, which indicates the severity of the inflammation, did not differ greatly between the sites. However, severe inflammatory cell infiltration of the aortic root, which is located near the coronary arteries, continued for a long time, compared to the thoracic aorta. Thus, the duration of inflammation varies with the site.

Next, while the inflammatory cells spread directly from the intima to the inner half of the media, the inflammatory cells infiltrated from the adventitial side to the outer half of the media. We investigated the involvement of the vasa vasorum in the progression of aortic inflammation in the media. The course of the vasa vasorum we observed is in agreement with an earlier report on the course of the vasa vasorum in the aorta of children [23], and that course is thought to represent the natural histology of the vasa vasorum in the aorta of children. On the other hand, in the migration
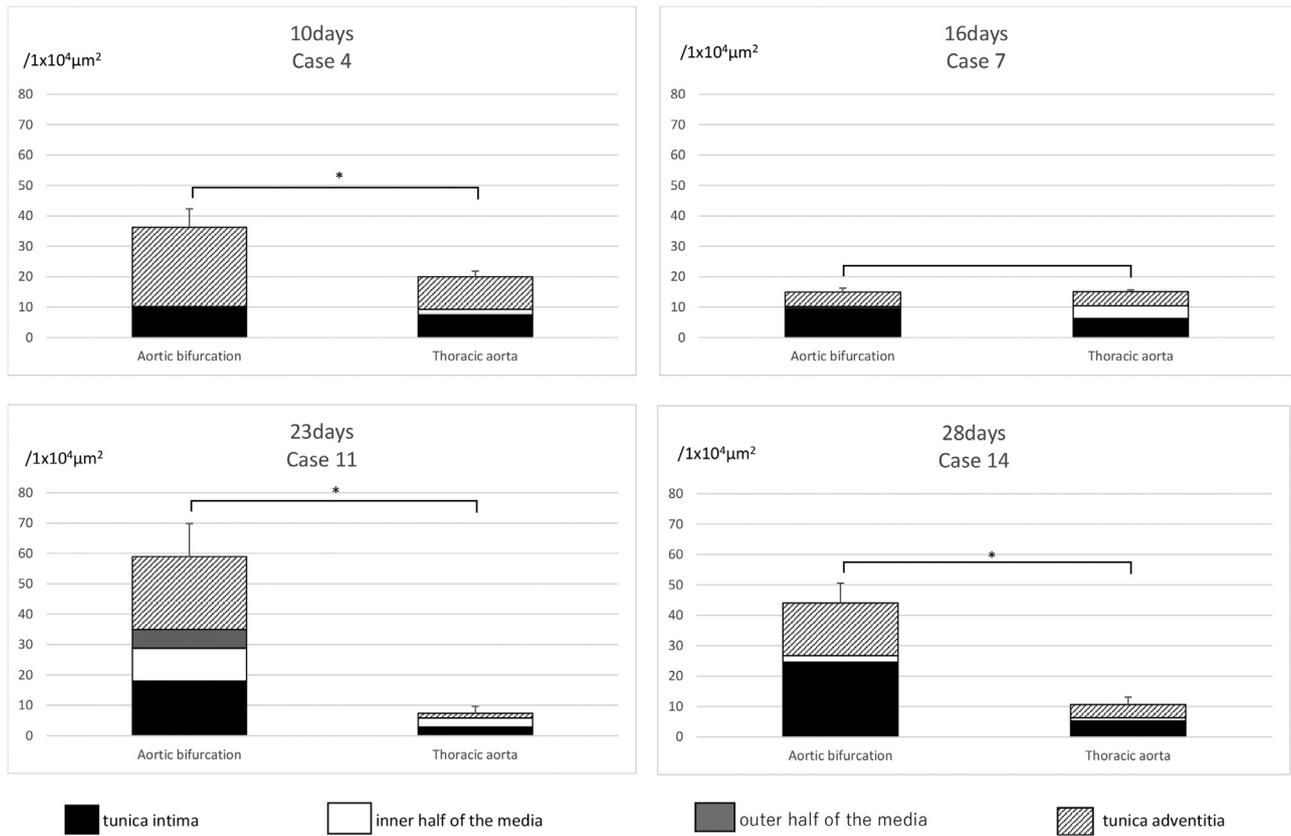
Fig. 6. Comparison of the aortic bifurcation and thoracic aorta (total number of inflammatory cells in each region). Comparison of the aortic bifurcation and thoracic aorta showed that, in 3 out of 4 cases, the degree of inflammatory cell infiltration was higher in the aortic bifurcation, especially in the tunica adventitia. * *P*<.01.
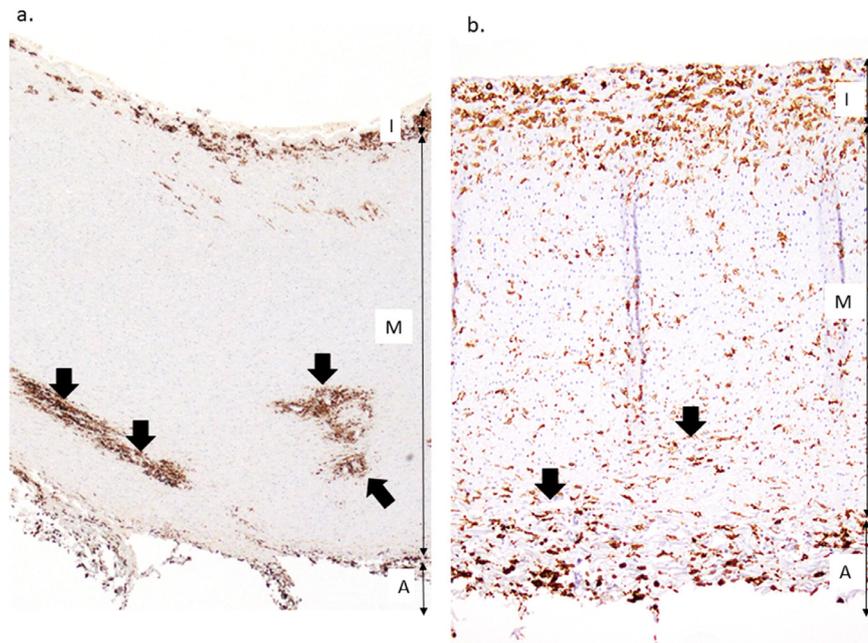

Fig. 7. CD163 The vasa vasorum in the aortic tunica media and the distribution of macrophages (CD163-positive) around it. Arrows: vasa vasorum; I: intima; M: media; A: adventitia. (a) Case 2, 10th disease-day. A high degree of macrophage infiltration is seen around the vasa vasorum. (b) Case 12, 24th disease-day. No aggregation of macrophages is seen around the vasa vasorum. Macrophages are invading the tunica media directly from the tunica adventitia.

of inflammatory cells to the outer side of the tunica media, there may be thus 2 modes: 1 in which progression of inflammation to the aorta's tunica media occurred via the vasa vasorum, and a second in which inflammatory cell infiltration of the tunica adventitia spread directly to the tunica media. The second mode is speculative because invasion of inflammatory cells around the vasa vasorum tended to be conspicuous in the early-phase death cases and the cases with diffuse infiltration tended to be seen in the late-phase. However, it was suggested that inflammatory cells spread directly from the adventitia to the media, because there were no images of transition between that and the diffuse infiltration pattern. It was reported that the density and distribution of the vasa vasorum differ between the ventral and dorsal sides of the aorta [23]. Thus, the mode of progression of inflammation may differ depending on the aortic site that is observed. Moreover, in all cases, we saw no vasculitis of the vasa vasorum or destruction of aortic elastic fibers around the vasa vasorum. This histological feature is clearly different from Takayasu arteritis [24,25], in which inflammation via the vasa vasorum destroys elastic fibers of the tunica media and causes granulomatous inflammation [24,25]!!!!. This shows that the pathogenesis is different between KD and Takayasu arteritis.

With regard to remote-phase lesions, we found that inflammatory cell infiltration of the aortic wall was extremely mild, and we found no destructive changes in the vascular architecture. In a majority of the acute-phase cases we examined, as well, the aortic architecture was preserved, even if there was inflammatory cell infiltration. This means that in many KD aortas, acute-phase inflammation resolves without leaving any scarring. A clinical study reported that the aortic pulse wave velocity was faster in remote-phase KD cases than in normal children and that the aorta of a patient with a history of KD may have a risk of arteriosclerosis as a post-inflammatory scar [26]. Our findings thus did not support that earlier report. However, when the vascular architecture is destroyed in acute-phase KD, structural and functional abnormalities of the vascular architecture wall caused by the inflammation persist even into the remote phase. This could be a long-term risk factor for atherosclerosis.

6. Limitations

This study has several limitations. First, it was difficult to standardize the conditions on the ventral and dorsal sides of the aorta, etc., because the details of the sampling sites for the specimens were unknown. Second, for some cases it was difficult to perform additional examinations such as immunostaining, etc., because of the limited size of the autopsied tissue block that was stored. Third, we used only 3 controls, which did not permit age-matching with all of the KD patients.

Author contributions

WS summarized the pathological findings, collected data and drafted the article. YY was involved in the conception of the study and participated in discussions. TO and NA were involved in interpretation of the data and participated in discussions. KT supervised all aspects of this study. All the authors read and approved the article.

Acknowledgments

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