

Original Article

Expression of tenascin C in cardiovascular lesions of Kawasaki disease

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ABSTRACT

Background/Objective: To examine tenascin C (TN-C) expression in coronary artery lesions (CALs) and myocardial lesions (MLs) in Kawasaki disease (KD).

Methods and Results: Twenty-five KD autopsy cases (post-KD-onset range of 6 days to 17 years) were examined in this study. Time-course analysis based on the disease day was performed of the histological findings for the CALs and MLs, as well as the localization and intensity of expression of TN-C. TN-C expression was observed to coincide with the areas where inflammatory cell infiltration was present in both coronary arteries and myocardium during the acute stage of KD, and the intensity of its expression correlated with the degree of inflammation. Obvious TN-C expression persisted in the thickened intima and media of CALs even after Disease Day 27. However, in spite of the presence of inflammatory cell infiltration, TN-C expression became weaker in the adventitia and surrounding connective tissue. After 8 months or more, TN-C was not expressed in the vasculitis scars of most cases, but expression was observed around newly formed vessels in the thickened intima and around recanalized vessels after thrombotic occlusion.

Conclusions: The findings suggest a correlation between the degree of inflammation and TN-C expression in the cardiovascular lesions of acute-stage Kawasaki disease.

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1. Introduction

Kawasaki disease (KD) is a systemic vasculitis that shows a predilection for manifesting in infants [1]. The highest incidence of involvement is seen with medium-sized muscular-type arteries, of which the coronary arteries are representative. The vasculitis leads to formation of aneurysms. Thrombotic occlusion occurs readily in aneurysms, and for this reason KD is an important disease that can lead to ischemic heart disease in childhood and adolescence. Coronary arteritis and also myocarditis are important complications of KD during its acute stage. Myocarditis, when including asymptomatic cases, is said to be a complication in upwards of 50% of KD patients, and it accounts for 10–15% of acute-stage mortality [2].

Abbreviations: TN-C, tenascin C; KD, Kawasaki disease; CALs, coronary artery lesions; MLs, myocardial lesions; IVIG, intravenous immunoglobulin; MMP, matrix metalloproteinase.

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Tenascin C (TN-C) is an extracellular matrix protein that regulates inflammation, angiogenesis, tissue repair and fibrosis [3,4]. TN-C is not expressed in the healthy coronary arteries or myocardium of adults or infants. However, when myocarditis, myocardial infarction, dilated cardiomyopathy and aortic aneurysms are present, the serum TN-C level is elevated and histopathological TN-C expression is seen to coincide with the location of the lesions. TN-C is thus considered to be a biomarker of acute inflammation in various cardiovascular diseases [5,6]. Recently, Okuma et al. [7] reported that serum TN-C could be a biomarker for predicting the risk of developing coronary artery lesions (CALs) and intravenous immunoglobulin (IVIG) resistance during the acute phase of KD. TN-C levels on admission were significantly higher in patients who later developed CAL than in patients who did not, and they were significantly higher in IVIG-resistant patients than in IVIG-responders. With this background, we performed a histopathological study to confirm whether TN-C is expressed in the coronary arteries and myocardium of KD patients.

2. Materials and methods

The study materials consisted of 25 autopsy cases of KD. The cases consisted of 18 males and 7 females, with an age range of 3 months to 20 years, and a post-KD-onset range of 6 days to 17 years. The day of

onset of a fever is defined as Disease Day 1. The present study was approved by the Ethics Committee of Toho University Ohashi Medical Center (H14-38, 27 August 2014).

2.1. Histological evaluation of myocardial lesions (MLs) and coronary artery lesions (CALs)

The heart was fixed in formalin and sliced horizontally, and the coronary arteries were excised. The coronary arteries were sectioned at 4-mm intervals in the peripheral direction from the aortic bifurcation. Hematoxylin and eosin (HE)-stained slides of the hearts and coronary arteries from each case were microscopically inspected. The myocardial lesions (MLs) were inspected for the degree and localization of inflammation and the presence of fibrosis. The degree of inflammation in the MLs was evaluated into three grades: none, mild or severe. The localization of inflammation was also evaluated into three grades: none, focal (1–50% of the myocardium of each section) or diffuse (51–100% of the myocardium of each section). For CALs, the most severe part of each lesion was examined by dividing it into “from the intima to the media” and “from the adventitia to the surrounding connective tissue”. The degree of inflammation in each portion of the artery was evaluated in the same way as for the MLs. The following evaluations were also performed: the presence/absence of dilation of the lumen of the coronary arteries, the presence/absence of fibrous thickening of the intima, and the presence/absence of recanalization after thrombotic occlusion.

2.2. Immunohistopathological study

Immunostaining of TN-C using a mouse monoclonal antibody 4F10TT, (IBL, Japan) was performed for the MLs and CALs of each KD autopsy case to investigate its degree of expression and localization. The degree of TN-C expression was evaluated into 3 grades: none, mild or severe. We identified the types of inflammatory cells by using CD3 as a T-cell marker, CD20 as a B-cell marker, CD66 as a neutrophil marker, and CD68 and CD163 as macrophage markers. α SMA was stained to elucidate the structure of the blood vessel walls. The names and sources of the antibodies are shown in Table 1.

2.3. Time-course study

Time-course analysis of TN-C expression in MLs and CALs was performed based on the disease day after onset of KD. Patients who died by the 40th disease day were defined as acute-stage KD cases. Patients who died later than that were defined as remote-stage cases. The reason for that threshold is that, histologically, the inflammatory cell infiltration of coronary arteritis usually disappears almost completely by the 40th day [8].

3. Results

3.1. Histological evaluation of MLs and CALs

Myocarditis was observed in seven of 11 acute-stage cases who died by Disease Day 33. In four of those seven cases, inflammatory cell infiltration was severe, with diffuse distribution in all examined myocardial

walls. No necrosis of cardiomyocytes was observed. In the remaining three cases, inflammatory cell infiltration of the myocardium was mild, with a focal distribution. The inflammatory cells were mainly monocytes/macrophages, but neutrophil infiltration was also prominent in acute-stage cases of up to Disease Day 20 (data not shown). Four of the 11 acute-stage cases had no cell infiltration of the myocardium. Furthermore, neither inflammatory cell infiltration nor post-inflammatory changes such as fibrosis or disarray of cardiomyocytes was seen in remote-stage cases (Table 2).

CALs were found in 23 of the 25 cases. Inflammatory cell infiltration was observed in the vascular wall of 13 cases between Disease Days 6 and 57, after which the inflammatory cells disappeared and fibrous thickening of the intima was observed (Table 3). Of the 23 cases with CALs, 20 cases showed formation of coronary aneurysms but the remaining three cases did not.

A Disease Day 6 case was observed to have localized, mild inflammation of the intima and adventitia, whereas in a Disease Day 10 case this had become panvasculitis due to inflammatory cell infiltration that involved all layers of the vessel wall. Panvasculitis was observed in cases from 10 through 38 disease days, and inflammation extended even to the perivascular connective tissue. The inflammatory cells were mainly macrophages, with some mixture of neutrophils and lymphocytes (data not shown). In a Disease Day 57 case, the inflammatory cell infiltration of all layers of the vessel wall showed a tendency to have dissipated, and inflammatory cell infiltration was no longer seen in a Disease Day 74 case. The intima of aneurysms became thickened due to fibrosis, and in two cases at 6 years and 17 years after KD onset there was recanalization of vessels.

3.2. TN-C expression

3.2.1. MLs (Table 2, Fig. 1)

The areas of TN-C expression in the myocardium coincided with the areas of inflammatory cell infiltration, and TN-C intensity correlated with the degree of inflammation in acute-stage cases. However, TN-C expression was not detected in areas of the myocardium with no inflammatory cell infiltration in acute-stage KD. No TN-C expression was detected in the myocardium of remote-stage cases.

3.2.2. CALs (Table 3, Figs. 2, 3)

TN-C expression was not detected in coronary arteries that had no vasculitis. In 13 acute-stage cases (i.e., up to Disease Day 40), TN-C expression coincided closely with the scope of inflammatory cell infiltration in the intima and media, and its intensity correlated with the degree of inflammation (Fig. 2: 1a–c, 2a–c, 3a–c, 4a–c). On the other hand, with regard to the adventitia and surrounding connective tissue, in four Disease Day 10–18 cases, strong TN-C expression was seen that coincided with the area of inflammatory cell infiltration (Fig. 2: 1a–c, 2a–c). But in five Disease Day 27–38 cases, expression tended to be weak in spite of a high degree of inflammatory cell infiltration (Figs. 2: 3a–c, 4a–c, 3a–f).

In remote-stage KD cases (i.e., Disease Day 41 and later), weak TN-C immunostaining was observed in the luminal surface of dilated aneurysms and in the thickened intima of recanalized vessels after thrombotic occlusion. No TN-C expression was detected in the adventitia or surrounding connective tissue (Fig. 2: 5a–c, 6a–c, 7a–c, 8a–c).

4. Discussion

TN-C is a protein that, like collagen, fibronectin, laminin, etc., is found in the extracellular matrix. However, TN-C is not involved in the formation of structures such as fibers and the basement membrane. Rather, it binds to cell surface receptors, growth factors, cytokines, proteases and other matrix molecules at the boundary between the cells and extracellular matrix, where it regulates interactions among the cells, extracellular factors and matrix fibers [3,4].

Table 1
Panel of antibodies used

Antigen	Antibody clone	Dilution	Source
CD3	Rabbit polyclonal	Prediluted	Dako
CD20	Mouse monoclonal, L26	Prediluted	Dako
CD66	Mouse monoclonal, kat4c	1:80	Dako
CD68	Mouse monoclonal PG-M1	Prediluted	Dako
CD163	Mouse monoclonal, 10D6	Prediluted	Leica Biosystems
SMA	Mouse monoclonal, 1A4	Prediluted	Dako
TN-C	Mouse monoclonal antibody, 4F10TT	Prediluted	IBL Japan

Table 2
TN-C expression in MLs

Case	Age	Sex	Day of disease	HE findings		TN-C expression	
				Degree of inflammation	Area of inflammation	Degree of TN-C expression	Area of TN-C expression
1	5y2m	M	6 d	+	focal	+	focal
2	3y	M	10 d	++	diffuse	++	diffuse
3	7m	M	14 d	-	none	-	none
4	3m	F	17 d	+	focal	+	focal
5	9m	M	18 d	-	none	-	none
6	1y10m	M	20 d	++	diffuse	++	diffuse
7	3m	M	27 d	-	none	-	none
8	1y7m	F	29 d	+	focal	+	focal
9	7m	M	30 d	++	diffuse	++	diffuse
10	2m	M	32d	-	none	+	focal
11	5m	M	33d	++	diffuse	++	focal
12	1y	M	36d	-	none	-	none
13	4m	M	38 d	-	none	-	none
14	1y6m	M	57 d	-	none	-	none
15	4y	F	74 d	-	none	-	none
16	5m	M	78 d	-	none	-	none
17	2y6m	M	87 d	-	none	-	none
18	8m	F	3 m	-	none	-	none
19	8m	F	5 m	-	none	-	none
20	2y	F	6 m	-	none	-	none
21	1y2m	F	8m	-	none	-	none
22	2y2m	M	1 y 2 m	-	none	-	none
23	9y	M	6 y	-	none	-	none
24	17y	M	13 y	-	none	-	none
25	20y	M	17 y	-	none	-	none

TN-C: Tenascin C; ML: myocardial lesion

In the heart, TN-C is transiently expressed very early in development, i.e., during the stages of differentiation into cardiomyocytes, formation of the endocardial cushion and valves, migration of coronary artery progenitor cells, etc. [9]. However, around the time of completion of formation of the atria and ventricles, no TN-C expression is seen, except around the developing coronary vessels. In adults, hardly any TN-C

expression is seen, but expression is known to accompany inflammation, wound healing, tissue regeneration and cancer invasion. TN-C is said to be produced by stromal cells, and it is also produced by vascular endothelial cells and vascular smooth muscle cells, as well as in the so-called fibroblasts of the stroma in diseased myocardial tissue. TN-C is degraded by such matrix-degrading enzymes as matrix

Table 3
TN-C expression in CALs

Case	Age	Sex	Day of disease	HE findings						TN-C expression		
				Acute inflammation of artery wall	Dilation /aneurysm	Degree of inflammation			Recanalized vessels	Intima	Media	Adventitia and surrounding connective tissue
						Intima and media	Adventitia and surrounding connective tissue	Fibrous thickened intima				
1	5y2m	M	6 d	+	-	+	+	-	-	+	-	-
2	3y	M	10 d	+	-	++	++	-	-	++	+	++
3	7m	M	14 d	+	+	++	++	-	-	++	++	++
4	3m	F	17 d	+	+	++	++	-	-	+	+	++
5	9m	M	18 d	+	+	++	++	-	-	++	++	++
6	1y10m	M	20 d	-	-	-	-	-	-	-	-	-
7	3m	M	27 d	+	+	++	++	-	-	++	++	+
8	1y7m	F	29 d	+	-	+	-	-	-	++	++	-
9	7m	M	30 d	+	+	++	+	-	-	+	+	+, f
10	2m	M	32 d	+	+	++	+	-	-	++	++	+, f
11	5m	M	33 d	+	+	++	++	-	-	+	++	+, f
12	1y	M	36 d	+	+	++	+	-	-	++	++	+
13	4m	M	38 d	+	+	++	+	-	-	++	++	+
14	1y6m	M	57 d	+	+	+	+	-	-	+	+	+, f
15	4y	F	74 d	-	-	-	-	-	-	-	-	-
16	5m	M	78 d	-	+	-	-	+	-	+	+	-
17	2y6m	M	87 d	-	+	-	-	+	-	+	+	-
18	8m	F	3 m	-	+	-	-	+	-	-	-	-
19	8m	F	5 m	-	+	-	-	+	-	++	+	-
20	2y	F	6 m	-	+	-	-	+	-	++	+	-
21	1y2m	F	8m	-	+	-	-	+	-	+	+	-
22	2y2m	M	1 y 2 m	-	+	-	-	+	-	-	-	-
23	9y	M	6 y	-	+	-	-	+	+	+	-	-
24	17y	M	13 y	-	+	-	-	+	-	+	-	-
25	20y	M	17 y	-	+	-	-	+	+	+	+	-

TN-C: Tenascin C; CAL: coronary artery lesion; f: focal

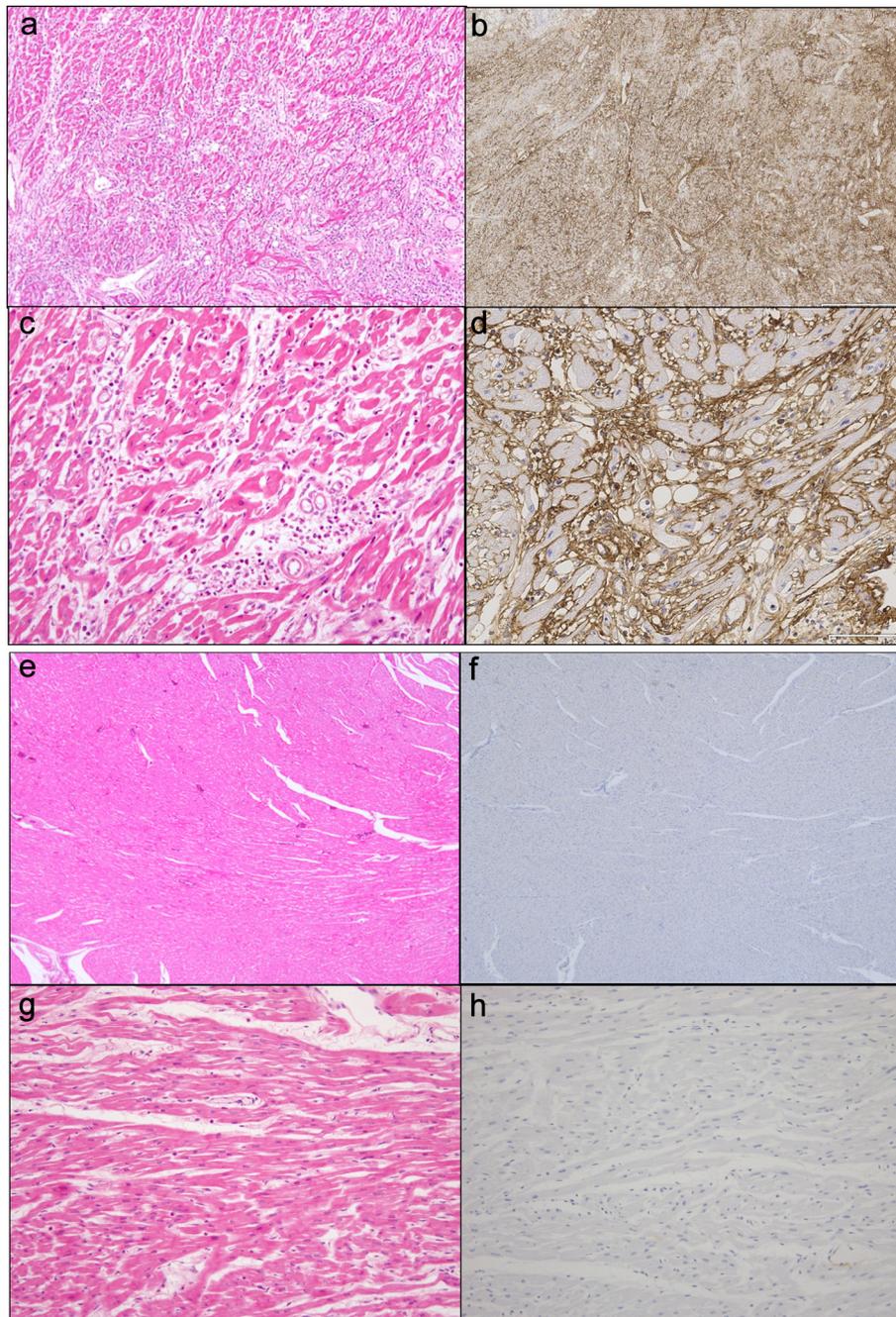


Fig. 1. TN-C expression in myocarditis. a–d, A Disease Day 10 case. Inflammatory cell infiltration is strong, and strong TN-C expression is seen at the same sites. e–h, Late-stage myocardial layers. There is no inflammatory cell infiltration or TN-C expression. (b,d,f,h: TN-C)

metalloproteinases (MMPs), etc., that are produced by macrophages and other cells [5]. The actions and effects of TN-C are complex, and it regulates cell functions via a variety of biological activities.

Expression of TN-C in the heart shows no disease or etiological specificity. It is expressed when there is tissue damage or inflammation, and also at times of active tissue remodeling. In myocarditis, expression of TN-C is localized around damaged cardiomyocytes in the early stage of lesion formation, expression continues as long as there are findings of active inflammation, and it finally disappears during the healing phase (formation of fibrotic scar foci). The level of TN-C expression correlates strongly with the degree of inflammation [10,11].

Our present study showed that TN-C expression in the myocardium of KD is similar to the expression that has been reported to date for myocarditis and that it matches the localization and degree of

inflammation seen in myocarditis. The inflammatory cells in the myocarditis of KD were reported to consist mainly of monocytes, macrophages and neutrophils [12], and our present results are in agreement with those earlier findings. The histopathological picture differs from that of viral myocarditis, which is comprised mainly of lymphocytes. However, the pattern of TN-C expression in KD myocarditis is similar to that reported for viral myocarditis [11]. Those results support the fact that TN-C expression shows no disease or etiological specificity. A study suggested that post-myocarditis changes, such as fibrosis, thickening and non-compaction, persist for a long time [13], while other reports emphasized that myocarditis in acute-stage KD resolved without sequela [13–15]. Our results support the latter because neither histological findings nor TN-C expression was observed in the myocardium of cases more remote than Disease Day 33.

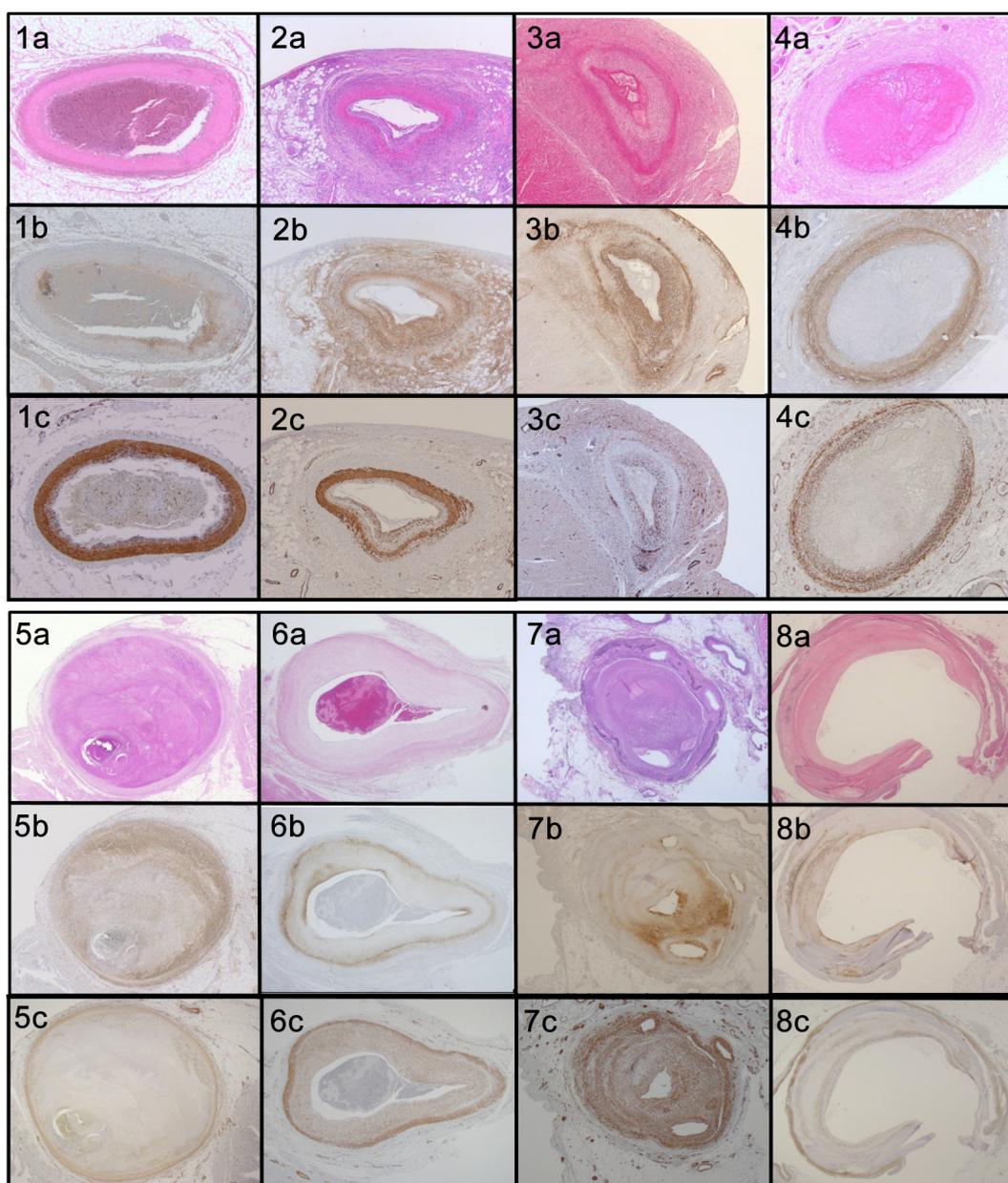


Fig. 2. CALs and TN-C expression. 1a, 1b, 1c: On Disease Day 6, inflammatory cell infiltration is seen to be confined to the intima and adventitia of the coronary arteries. TN-C expression coincides with that but is weak in intensity. 2a, 2b, 2c: On Disease Day 18, a high degree of inflammatory cell infiltration is seen in all arterial wall layers and in the surrounding tissue, and the intensity of TN-C expression shows strong agreement with those sites. 3a, 3b, 3c: On Disease Day 33, a high degree of inflammatory cell infiltration is seen in all arterial wall layers and in the surrounding tissue. TN-C expression is seen in the intima and media, but it is now attenuated in the surrounding tissue. 4a, 4b, 4c: On Disease Day 38, inflammatory cell infiltration is seen in the intima, but there is a tendency for inflammatory cell infiltration in the surrounding tissue to have disappeared. TN-C expression is seen in the intima and media, but it is weak in intensity in the surrounding tissue. 5a, 5b, 5c: On Disease Day 57, thrombus formation is seen in the lumen. Inflammation in the surrounding tissue has disappeared. TN-C expression is seen in the intima and media, but not in the surrounding tissue. 6a, 6b, 6c: On Disease Day 87, inflammatory cell infiltration has disappeared completely from all layers, and TN-C expression is seen in the thickened intima and media. 7a, 7b, 7c: After 6 years, TN-C expression is seen in the thickened intima and in the intimal surface of recanalized vessels. 8a, 8b, 8c: After 13 years, TN-C expression is seen in the thickened intima. (7a: Elastica-HE. 1b, 2b, 3b, 4b, 5b, 6b, 7b, 8b: TN-C, 1c 2c, 3c, 4c, 5c, 6c, 7c, 8c: α SMA)

As for TN-C expression in the vascular lesions, histopathological examinations were performed only for human abdominal aortic aneurysms [16]. Those tissues showed two characteristic pathological changes: inflammatory cell infiltration consisting mainly of lymphocytes and macrophages, and destruction of the aneurysm's extracellular matrix, especially the elastic fibers. Whereas almost no TN-C expression was seen in control aortic tissues having no dilated changes, the expression was up-regulated in aortic aneurysm tissues with pronounced inflammatory cell infiltration accompanied by elastic fiber destruction.

In the CALs of KD, the inflammatory cells were reported to consist mainly of macrophages and neutrophils [17], our present results are in agreement with those earlier findings. Interestingly, our findings

revealed that, in the CALs of KD, the TN-C expression patterns differ in the vascular intima and media, and in the adventitia and surrounding connective tissue, as a function of the time since onset of KD. In the intima and media, TN-C expression coincided with the sites and degree of inflammation in cases of KD up to Disease Day 57. In the adventitia and surrounding connective tissue of KD cases from Disease Day 27–57, TN-C expression was attenuated even though there was inflammatory cell infiltration comprised mainly of macrophages. The attenuation of TN-C expression in the adventitia and surrounding connective tissue of the coronary arteries occurs earlier than on the intimal side, even though HE-stained specimens showed a similar degree of inflammatory cell infiltration at both locations. That might be due to differences in the

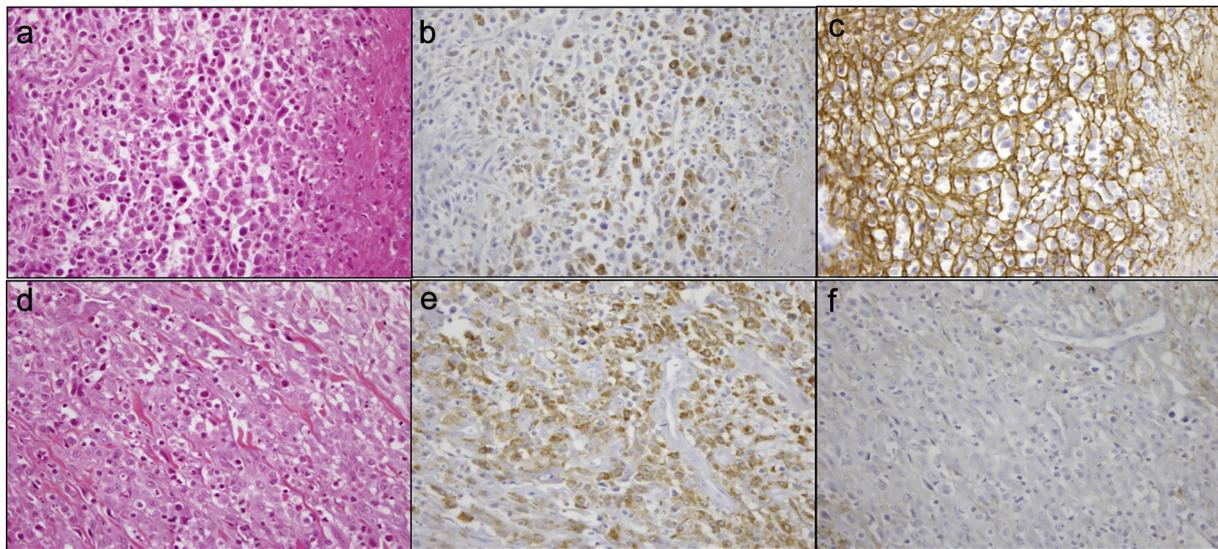


Fig. 3. In a Disease Day 33 case, TN-C expression is seen in the intima and medial side, but not seen in the adventitia and surrounding connective tissue. a–c: There is a high degree of inflammatory cell infiltration in the intima and media, and TN-C expression is seen. d–f: Adventitia and surrounding connective tissue. CD163-positive macrophages are numerous, but TN-C expression is not seen. (b, e: CD163; c, f: TN-C)

numbers of fibroblasts and smooth muscle cells that produce TN-C and differences in the phenotypes of the macrophages that produce MMPs that degrade TN-C between the internal and outer sides of the coronary arteries. Recently, a report indicated that macrophages can be classified into several phenotypes, and the phenotypes are basically different between monocyte-derived macrophages and tissue-resident macrophages [18]. The phenotypes of macrophages might differ with the vascular site. We are performing further studies to elucidate phenotype differences among macrophages appearing in the CALs in KD.

In the remote stage of KD, inflammatory cells disappeared from all vascular tissue layers, but TN-C expression was observed in the intimal surface of thickened intima and around recanalized vessels. These results can be thought to reflect tissue remodeling.

In conclusion, TN-C expression was confirmed even in the cardiovascular lesions of KD. The findings suggest a correlation between the degree of inflammation and TN-C expression in the cardiovascular lesions of acute-stage Kawasaki disease.

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