Pediatr Cardiol 22:138–142, 2001
DOI: 10.1007/s002460010180

Pediatric Cardiology

Pathological Study of Postcoronary Arteritis in Adolescents and Young Adults: With Reference to the Relationship Between Sequelae of Kawasaki Disease and Atherosclerosis

K. Takahashi, T. Oharaseki, S. Naoe

Department of Pathology, Ohashi Hospital, Toho University School of Medicine, 2-17-6 Ohashi, Meguro, Tokyo, 153-8515, Japan

Abstract. To clarify whether the cardiac sequelae of Kawasaki disease (KD), postcoronary arteritis lesions can become a risk factor for atherosclerosis of the coronary arteries, six autopsy cases of patients older than 15 years of age with coronary arterial lesions caused by arteritis in childhood were examined histologically. Twenty-four arteries were inspected: 10 had no evidence of aneurysm formation, 7 arteries manifested simple dilatation of the lumen, and in 7 arteries there were aneurysms with recanalization. In the group in which there were no aneurysms, "new intimal thickening" was observed in addition to the preexisting intimal thickening which had been caused by arteritis in the acute phase of KD. In the second group with aneurysmal arteries whose lumen remained dilated, thrombotic occlusion occurred in 4 of 6 aneurysms. In addition, advanced atherosclerotic changes (i.e., complicated lesions) were found in a 39-year-old patient. Finally, in the third group of arteries which manifested recanalized lumens after thrombotic occlusion of the aneurysms, new intimal thickening was seen on the internal side and some of them were occluded. The findings in this study suggest that aneurysms present in coronary arteries in individuals with a history of KD constitute a risk factor for atherosclerosis later in life.

Key words: Kawasaki disease — Coronary arteritis — Coronary artery aneurysm — Atherosclerosis — Pathology

Kawasaki disease (KD), an acute febrile illness of infants and young children, is a systemic vasculitis syndrome. It is estimated that coronary arteritis is caused in the majority of patients by acute KD [10]. The etiology of KD is unknown and its diagnosis is based on clinical signs. Current treatment consists of intravenous gamma-globulin and high-dose aspirin. In recent years, the death rate from KD has decreased to 0.1%, but cardiac sequelae continue to manifest in about 13% of KD patients [20, 21]. The increased incidence in adolescents and young adults who experience KD during childhood has been accompanied by a new problem of an association between post-KD lesions and atherosclerosis [7, 19]. Therefore, a histopathological study was carried out in an attempt to elucidate whether the presence of postarteritis changes can become a risk factor for atherosclerosis of the coronary arteries.

Correspondence to: K. Takahashi

Materials and Methods

The experiment consisted of six autopsy patients with sequelae of coronary arteritis who died after the age of 15 years. These cases included four males and two females. Their ages at death ranged from 15 to 39 years (Table 1). Three of these cases had a confirmed history of KD. The history of KD could not be confirmed in the other three cases. However, they were found to have giant saccular coronary artery aneurysms at the time of autopsy. Histological findings of the aneurysms in these three patients could not be distinguished from those seen in KD. It is very likely that KD affected these three cases during childhood and arteritis had been involved in the development of these aneurysms. These six autopsy cases were considered to be appropriate for the objective of the current study to clarify the association between postarteritis lesions and atherosclerosis.

The tissues were fixed in 10% formalin and embedded in paraffin. Hematoxylin and eosin stain (HE), Elastica van Gieson stain, azan-Mallory stain, and Elastica–HE stain were performed for routine histological examination. Immunohistological staining by the avidin–biotylated peroxidase complex method was performed on the paraffin sections using anti-human macrophage monoclonal antibody (HAM-56, DAKO Japan Co., Ltd.).

Each of the cases was inspected for aneurysms of the left main coronary trunk (LMT), left anterior descending coronary artery, left circumflex coronary artery (LCX), and right coronary artery. If an aneurysm was present, it was classified as either a simply dilated artery or a recanalized artery after thrombotic occlusion. Next, each blood vessel was inspected to determine if there was further progression of

Table 1. Six autopsy cases of patients older than 15 years of age who had postarteritis lesions in coronary arteries

Case no.	Age (years)	Sex	Occupation	History and course
1	15	M	Student	1 year old: Kawasaki disease Died secondary to staphylococcal pneumonia and sepsis
2	15	F	Student	1 year old: atopic dermatitis; 10 years old: bronchial asthma Sudden death
3	19	M	Student	3 years old: Kawasaki disease Sudden death
4	20	F	Office worker	5 and 7 years old: acute febrile disorder, details unknown; 17 years old: arrhythmia Sudden death
5	20	M	Student	4 years old: Kawasaki disease Sudden death
6	39	M	Office worker	20 years old: cardiac hypertrophy with history for heart failure Sudden death

F, female; M, male.

the intimal thickening, and the thickening was evaluated in terms of its severity and its structural components, especially as to whether foamy macrophages were present. It was noted that even in arteries with no aneurysm, there is thinning of the tunica media and concentric thickening of the intima with a new, internal elastic lamina-like structure on the inner luminal surface (Fig. 1). Our studies to date have indicated that these findings correspond to postinflammatory changes and occur years after the development of KD [9, 13]. Thus, in the current study we carried out further inspection of the inner thickening of the intima. Since each of the recanalized arteries showed a structure similar to that of normal arteries within a few years after the onset of KD [14, 15], we inspected these arteries to determine whether or not there had been new intimal thickening.

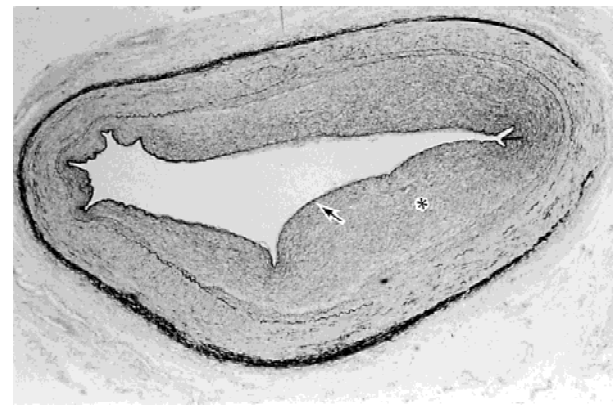

Fig. 1. Postarteritis changes seen in right coronary artery of case 1 who died 14 years after the development of KD. Thinning of the tunica media and concentric intimal thickening (*) with a new internal elastic lamina-like structure (arrow) were observed. Since these changes occur years after the development of KD [7, 8], we carried out further inspection of the inner thickening of the intima.

Results

Arteries with No Evidence of Aneurysm Formation

Ten of 24 inspected arteries showed no formation of an aneurysm, and new intimal thickening was seen in 7 of the 10 arteries. In most cases, the new thickening was localized, and it was composed of fibrotic tissue having a low cell density. In the LCX of case 5 (20-year-old male), a bright area was seen in the deep part of the newly formed intimal thickening and small aggregations of foamy macrophages could also be seen in this area (Fig. 2). In the LCX of case 6 (39-year-old male), the formation of an atheroma with many macrophages was observed in the deep layer of the new intimal thickening. However, none of the 10 arteries, without the formation of an aneurysm, were accompanied by narrowing of the arterial lumen.

Aneurysms which Display Simple Dilatation of the Lumen

Seven arteries showed aneurysms which displayed simple dilatation of the lumen. In four of these arteries, the lumen of the aneurysm was filled with a thrombus. In an artery of case 2 (15-year-old female), aggregations of foamy macrophages were seen in the intima where it contacted the thrombus. In the LMT of case 6, together with a mixture of new and old thrombi, aggregations of macrophages and a high degree of formation of atheroma containing cholesterol crystals were seen (Fig. 3). In lesions with striated calcification in the wall of the aneurysm, the innermost side of the lesion showed edematous new intimal thickening. No cellular components were observed in the new intimal thickening in an artery of case 3 (19-year-old male). In contrast, numerous HAM-56 positive macrophages were observed in the new intimal thickening of an artery of case 6. Furthermore, at the ostium of the left coronary artery of case 6, intimal thickening accompanied by ulceration was seen. This intimal

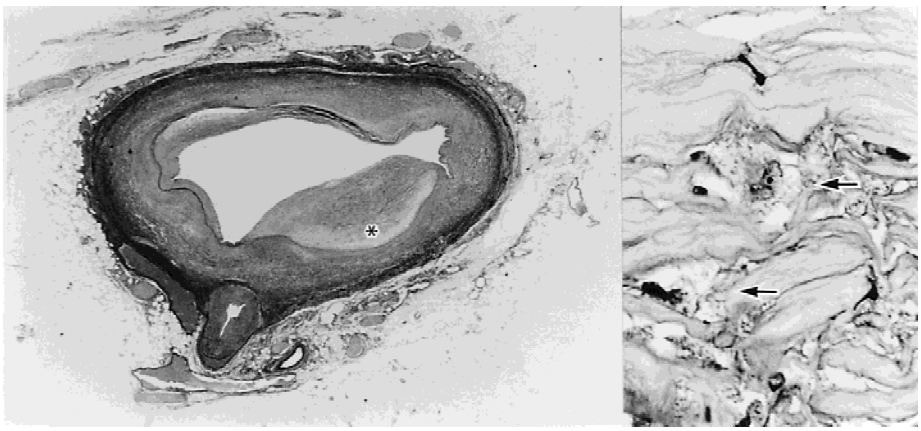

Fig. 2. Arteries with no formation of an aneurysm. Newly formed intimal thickening (*) and a small amount of foam cells in that area (arrows) are shown (LCX of case 5) (Elastica–HE: *left;* ×20, *right;* ×400).

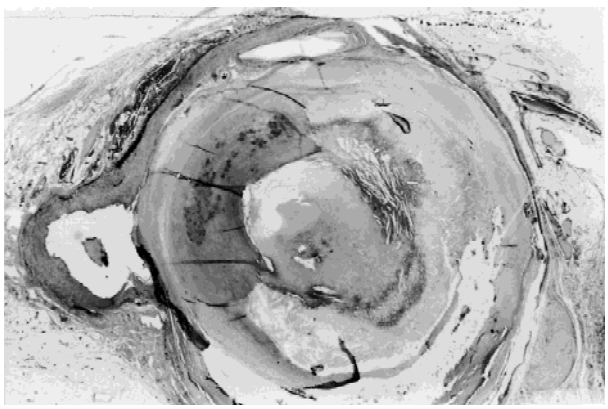

Fig. 3. The lumen of the aneurysm was filled with thrombi, containing aggregation of macrophages and cholesterol crystals (LMT of case 6) (Elastica–HE, ×10).

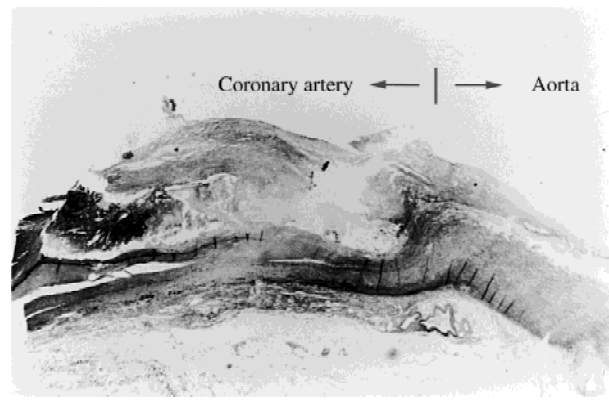

Fig. 4. Complicated atherosclerotic lesion in the orifice of the left coronary artery of case 6 (Elastica–HE, ×10).

thickening was observed to contain atherosclerotic lesions which correspond to complicated lesions consisting of atheroma and macrophages, hemorrhage, microcalcification, etc. (Fig. 4).

Aneurysms with Recanalization

There were seven coronary arteries which had been recanalized, all of which showed new intimal thickening. In case 2 and case 4 (20-year-old female), all the recanalized arteries also showed intimal thickening, and some of the arteries had progressed to occlusion. Most of the new intimal thickening in the recanalized arteries was composed of fibrocellular elements. However, foamy macrophages were also seen in the thickened intima of recanalized arteries in case 5 and in case 6 (Fig. 5). These results are summarized in Table 2.

Discussion

KD was first described as acute febrile mucocutaneous lymph node syndrome (MCLS) by Dr. Tomisaku Kawasaki in 1967 [4]. This disease is one of the systemic vasculitis syndromes. KD has attracted special interest because death from this disease is most frequently attributable to ischemic heart disease caused by thrombosed coronary artery aneurysms, secondary to coronary arteritis [1, 5, 18]. On the other hand, we report pathological observation of patients who had a history of KD and died of traffic accidents or malignant tumors [10]. These patients had no symptoms of ischemic heart disease while alive and no coronary artery aneurysm was found at autopsy, but lesions of coronary arteritis were seen. Current therapy for prevention of coronary artery abnormalities in KD consists of intravenous gamma-globulin and high-dose aspirin. The mortality rate, as well as the incidence of coronary artery abnormalities, has decreased after intravenous gamma-globulin therapy, but cardiac sequelae continue to be manifest in about 13% of KD patients [20, 21]. As the number of patients who experience KD increases, new problems of long-term coronary damage must be considered. How does atherosclerosis affect postinflammatory arteries when patients who had experienced KD during childhood become adults? It is very

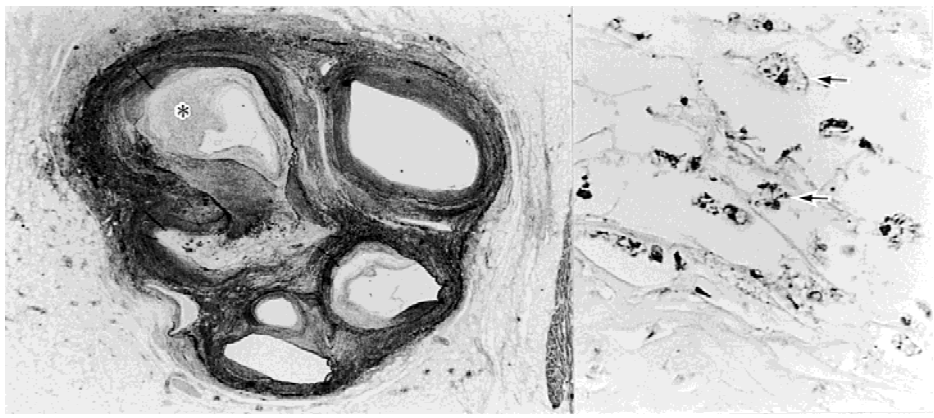

Fig. 5. Recanalized aneurysm. Anti-human macrophage antibody positive cells (arrows) were seen in the new intimal thickening of the recanalized arteries (*) (RCA of case 6) (*left:* Elastica–HE, ×10; *right:* HAM-56, ×400).

Table 2. Pathological findings of the coronary arteries

Case No.	Age (years)	Sex	Artery	Thrombi	NIT	Macrophage	Calcification
			Arteries with no formation of an aneurysm				
1	15	M	LMT	−	+	−	—
1	15	M	LAD	−	−	−	—
1	15	M	LCX	−	−	−	—
1	15	M	RCA	−	−	−	—
3	19	M	LCX	−	+	−	—
3	19	M	RCA	−	+	−	—
4	20	F	LMT	−	+	−	—
4	20	F	LCX	−	+	−	—
5	20	M	LCX	−	+	+	Minute
6	39	M	LCX	−	+	++	Minute
			Aneurysms with simple dilatation of the lumen				
2	15	F	LMT	+	−	−	—
2	15	F	LAD	+	−	+	—
2	15	F	RCA	+	−	−	Minute
3	19	M	LMT	−	+	−	Circular
3	19	M	LAD	−	+	−	Circular
5	20	M	RCA	−	+	−	Circular
6	39	M	LMT	+	+	++	Circular
			Aneurysms with the recanalized arteries				
2	15	F	LCX	−	+	−	—
4	20	F	LAD	−	+, stenosis	−	Minute
4	20	F	RCA	−	+, stenosis	−	Minute
5	20	M	LMT	−	+, stenosis	−	Massive
5	20	M	LAD	−	+, stenosis	+	Massive
6	39	M	LAD	−	+, stenosis	+	Minute
6	39	M	RCA	−	+, stenosis	+	Massive

F, female; M, male; LMT, left main coronary trunk; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; NIT, new intimal thickening.

important to examine the association between postcoronary arteritis lesions and atherosclerosis, but to date studies have not been very revealing. In this study, in attempt to resolve this problem, we selected six autopsy patients who died when older than 15 years of age and carried out histological examination of the postcoronary arteritis lesions. In three of these cases, a history of KD could not be confirmed. These saccular aneurysms were frequently observed in the proximal site of coronary arteries, and the results of histological examination indicated lesions

of panarteritis (i.e., marked thinning of the tunica media, destruction of the internal elastic lamina, and fibrosis in the adventitia) were seen in the lesions. These histological findings could not be distinguished from those of KD [6, 8, 11]. These cases very likely experienced KD during childhood. They might have developed severe coronary arterial abnormalities following febrile illnesses which did not fulfill classic KD diagnostic criteria clinically. Actually, ischemic heart disease in young adults as a result of undiagnosed KD in childhood is increasingly recognized by cardiologists [2, 3].

We found, in the 15-year-old patient, no aneurysms or recanalized arteries, but new intimal thickening was present. Foamy macrophages were observed in the 20-year-old and the 39-year-old patients, and the cellular infiltration was severe in the latter. Some recanalized arteries showed occlusion of the lumen. Furthermore, in the 39-year-old patient, severe atherosclerotic lesions were seen in arteries with aneurysm formation.

On the other hand, in a nationwide study using published autopsy cases for arteriosclerotic lesions of the coronary arteries of Japanese, it was documented that fatty streaks (i.e., early atherosclerotic lesions) are seen in 30% of people in their twenties and 40% of people in their thirties, whereas fibrous plaques are seen in about 15% of people in their twenties or thirties. However, complicated lesions have been said to occur in only 1% of people even in their thirties [2, 17]. Furthermore, although there are some reports that coronary artery aneurysms develop as a result of coronary arteritis affected by inflammatory diseases such as polyarteritis nodosa or systemic lupus erythematosus [16], we could not find any reports of coronary artery aneurysms caused by atherosclerosis in patients less than 40 years of age in Japan.

In this study, most of the fatty deposits which were seen were considered to correspond to mild, early atherosclerotic lesions. However, ulcerative lesions at the aneurysm site in the 39-year-old patient were judged to be severe atherosclerotic lesions. Thus, we surmise that at least when aneurysms are present, a history of KD in childhood becomes a risk factor for atherosclerosis later in life.

Acknowledgments. We thank our colleagues in the Department of Pathology, Ohashi Hospital, Toho University School of Medicine for helpful discussions. This work was supported in part by project research grant No. 7-7 from Toho University School of Medicine; a grant-in-aid for scientific research from the Ministry of Education, Science and Culture, Japan (No. 10770087); and a research grant from the Japan Kawasaki Disease Research Center.

References

1. Fetterman GH, Hashida Y (1974) Mucocutaneous lymph node syndrome (MLNS): a disease widespread in Japan which demands our attention. *Pediatrics 54*:268–270
2. Fineschi V, Paglicci RL, Baroldi G (1999) Coronary artery aneurysms in a young adult: a case of sudden death. A late sequelae of Kawasaki disease? *Int J Legal Med 112*:120–123
3. Kato H, Inoue O, Kawasaki T, et al. (1992) Adult coronary artery disease probably due to childhood Kawasaki disease. *Lancet 340*: 1127–1129
4. Kawasaki T (1967) Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of fingers and toes in children. Clinical observation of 50 patients. *Jpn J Allergy 16*:178–222
5. Kawasaki T, Kosaki F, Okawa S, Shigematsu I, Yanagawa H (1974) A new infantile acute febrile mucocutaneous lymph-node syndrome (MLNS) prevailing in Japan. *Pediatrics 54*:271–276
6. Masuda H, Naoe S, Tanaka N (1981) A pathological study of coronary artery in Kawasaki disease (MCLS)—with special reference to morphogenesis of aneurysm. *J Jpn Coll Angiol 21*: 899–912
7. Naoe S, Masuda H (1981) Kawasaki disease as a risk factor of juvenile arteriosclerosis. *J Jpn Arteriosclerosis Soc 9*:27–35
8. Naoe S, Shibuya K, Takahashi K, et al. (1991) Pathological observations concerning the cardiovascular lesions in Kawasaki disease. *Cardiol Young 1*:212–220
9. Naoe S, Takahashi K (1993) Kawasaki disease with the focus on sequelae. In: Tanabe T (ed) *Intractable Vasculitis Syndromes.* Hokkaido University Press, Sapporo, Japan, pp 93–103
10. Naoe S, Takahashi K, Masuda H, Tanaka N (1987) Coronary findings post Kawasaki disease in children who died of other causes. In: Schulman ST (ed) *Kawasaki Disease.* Liss, New York, pp 341–346
11. Naoe S, Takahashi K, Masuda H, Tanaka N (1991) Kawasaki disease with particular emphasis on arterial lesions. *Acta Pathol Jpn 41*:785–797
12. Sakurai I, Miyakawa K, Komatsu A, Sawada T (1990) Atherosclerosis in Japanese youth with reference to differences between each artery. *Ann NY Acad Sci 598*:410–417
13. Takahashi K, Hirota A, Naoe S, et al. (1991) A morphological study of intimal thickening in sequelae of coronary arterial lesions of Kawasaki disease (1). *J Jpn Coll Angiol 31*:17–25
14. Takahashi K, Naoe S (1994) Histopathological study of recanalized vessels in sequelae of coronary arterial lesions of Kawasaki disease. *Acta Cardiol Paediatr Jpn 10*:233–240
15. Takahashi K, Shibuya K, Masuda H, Tanaka N (1989) A histopathological study on cardiac sequelae of Kawasaki disease. *J Jpn Coll Angiol 29*:461–469
16. Takahashi M (1993) Inflammatory disease of coronary artery in children. *Coronary Artery Dis 4*:133–138
17. Tanaka K, Masuda J, Imamura T (1988) A nation-wide study of atherosclerosis in infants, children and young adults in Japan. *Atherosclerosis 72*:143–156
18. Tanaka N (1975) Kawasaki disease (acute febrile infantile mucocutaneous lymph node syndrome) in Japan: relationship with infantile periarteritis nodosa. *Pathol Microbiol Basel 43*:204–218
19. Tanaka N, Naoe S, Masuda H, Ueno T (1986) Pathological study of sequelae of Kawasaki disease (MCLS) with special reference to heart and coronary arterial lesions. *Acta Pathol Jpn 36*:1513–1527
20. Yanagawa H, Tuohong Z, Oki I, et al. (1999) Effects of gammaglobulin on the cardiac sequelae of Kawasaki disease. *Pediatr Cardiol 20*:248–251
21. Yanagawa H, Yashiro M, Nakamura Y (1998) 14th nationwide survey on Kawasaki disease. *J Pediatr Practice 61*:406–420