PATHOLOGY OF KAWASAKI DISEASE:

I. PATHOLOGY AND MORPHOGENESIS OF THE VASCULAR CHANGES

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Histopathological investigation of the vascular changes in Kawasaki disease was carried out on thirty-seven autopsied Japanese patients.

Arterial lesions could be classified into following five stages from the view point of morphogenesis of arteritis; 1) endothelial degeneration and increased vascular permeability, 2) edema and degeneration of the media, 3) necrotizing panarteritis, 4) granulation formation, and 5) scarformation. Aneurysm with thrombus was observed mainly in the coronary artery in most patients. It is considered that the initial changes begins in the endothelial cells with increased vascular permeability.

Platelet aggregation in the damaged endothelial cells seems to play an important role in the further development of the arteritic changes.

Vascular lesions were observed not only in the arterial system but also in the venous system, therefore Kawasaki disease is a systemic vasculitis rather than a systemic arteritis.

KAWASAKI disease (acute mucocutaneous lymph node syndrome, MCLS), described for the first time by Dr. T. Kawasaki, affects children mainly under four years of age and is characterized by several definite clinical manifestations.¹ More than 10,000 patients with this syndrome have been reported in Japan since the first report in 1967.² Death in 1.7% of all patients is mostly due to cardiac lesions. Pathological investigation of autopsied cases disclosed a necrotizing arteritis, which is similar to infantile

periarteritis nodosa.³ Relationship between Kawasaki disease and infantile periarteritis nodosa or the independency of Kawasaki disease has been reported.³⁻⁶ There is apparently no systemic pathological study on the vascular changes in this disease except for the report of Tanaka et al.³ Several sporadic case reports have been documented.^{4,7,8} The present study was an attempt to clarify the pathology and morphogenesis of the vascular lesions of Kawasaki disease.

MATERIALS AND METHODS

Vascular changes were systematically studied, using histopathological method, in 37 autopsied Japanese patients. Age, sex, duration of the disease and clinical diagnosis of each patient are

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Key Words:

Kawasaki disease
Vasculitis
Pathology and morphogenesis
Endothelial cell

(Received on January 8, 1979; Accepted on March 13, 1979)

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Supported by a Grant from the Systemic Vascular Disease Research Committee, Ministry of Health and Welfare, Japan.

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TABLE I AUTOPSIED PATIENTS OF KAWASAKI DISEASE

Name	Sex	Age	Duration of disease	Clinical diagnosis
1) R.M.	M	10M	9 days	MCLS
2) T.Y.	M	1Y 8M	10	s.o. MCLS
3) M.H.	M	2Y	12	MCLS
4) T.Y.	M	1Y 5M	17	subsepsis allergica
5) M.I.	M	6M	17	influenza
6) Y.M.	M	3M	18	MCLS
7) M.N.	M	1Y 6M	18	MCLS
8) T.S.	M	3Y	19	MCLS
9) T.H.	M	5Y 11M	19	MCLS
10) M.G.	F	4M	19	MCLS
11) H.S.	F	5M	19	MCLS
12) X.Y.	M	6M	20	acute heart failure
13) A.N.	M	4M	21	s.o. MCLS
14) H.I.	M	1Y 8M	24	sepsis
15) S.N.	M	1Y	26	s.o. MCLS
16) Y.T.	M	6M	27	MCLS
17) T.S.	M	10M	31	MCLS
18) C.T.	F	1Y 6M	31	myocarditis
19) Y.T.	F	7M	31	MCLS
20) F.Y.	M	6M	32	MCLS
21) T.K.	M	11M	34	MCLS
22) H.I.	M	5M	36	Izumi fever
23) T.K.	M	1Y	36	MCLS
24) K.F.	F	7M	40	MCLS
25) H.K.	M	4M	43	invagination
26) A.H.	M	4M	44	?
27) K.E.	F	9M	49	MCLS
28) Y.S.	M	9M	60	MCLS
29) H.M.	M	1Y 1M	66	MCLS
30) N.S.	M	10M	78	infectious disease
31) Y.H.	F	2Y	6 months	MCLS
32) M.S.	F	1Y 3M	11	MCLS
33) T.T.	M	5Y 1M	1 year 1 month	measles
34) N.I.	M	6Y 6M	2 years	s.o. MCLS
35) S.K.	M	4Y 6M	3	myocarditis
36) T.Y.	M	4Y 5M	4	MCLS
37) T.H.	M	5Y	4 years 6 months	MCLS

shown in the Table I. Blood vessels investigated included: 1) large elastic and musculoelastic arteries (the aorta, carotid, subclavian, celiac, iliac and main pulmonary arteries), 2) middle sized arteries of the extraviscera (the main coronary, intercostal, hepatic, splenic, mesenteric, renal and lumbar arteries), 3) arteries of the intraviscera (in the tongue, salivary gland, lung, gastrointestinal tracts, spleen, pancreas, liver, kidney, testis or ovary, and skin), and 4) the venous system.

Hematoxylin and eosin staining was used for

the routine observation, and elastica van Gieson and phosphotangustic acid hematoxylin stainings were utilized as required.

RESULTS

Arterial lesions were categorized according to the degree of inflammatory changes and to the duration of the disease. Six characteristic types of lesions were identified in the arterial system.

Type one (Degeneration of the endothelial cells)

In the endothelial cells, swelling and prolifera-

Fig.1. Endothelial cells showed hyperplastic, proliferative and degenerative changes. Desquamation of the endothelial cells is also visible. Subendothelial space and inner media are edematous. Renal artery. Case No.1 H & E $\times 200$

Fig.2. Small fresh thrombus consisted of aggregated platelets, inflammatory cells and fibrin along the degenerated and desquamated endothelial cells. Mesenteric artery. Case No.1 H & E $\times 100$

Fig.3. Mild inflammatory infiltration is present in the edematous, thickened intima. Vacuolization of the muscle cells and edema of the media are remarkable. Mesenteric artery. Case No.5 H & E $\times 200$

tion were evident, the nuclei were in general enlarged and degeneration and desquamation were frequently observed (Fig. 1). Fibrin mass including platelets and inflammatory cells was frequently seen to be attached to such degenerated parts forming a minute parietal thrombus (Fig. 2). In the subendothelial space beneath such lesions, there were mild edematous changes. The internal elastic lamina was swollen and acidophilic.

Sometimes scant inflammatory infiltration consisting of lymphocytes, large mononuclear cells and neutrophils was observed in the endothelial cell line or subendothelial spaces. In the inner portion of the media, vacuolization of the smooth muscle cells and edema were also seen to a mild degree. Edema and mild inflammatory infiltration consisting of the same cells as seen in the intima were observed in the adventitia.

In the perivascular area, around capillaries, venules or lymphatics, a small number of inflammatory cells was also seen. In larger arteries with vasa vasorum, the endothelial cells of the vasa vasorum were also swollen and small foci of edema with mild inflammatory infiltration were present in the arterial wall along the vasa vasorum. Endothelial cell changes with mild inflammatory cell reaction and edema were the

characteristic features of this type of vascular lesion.

Type two (Edema and degeneration of the media)

In addition to the changes in the intima seen in the type one, small or moderate number of lymphocytes, large mononuclear cells and neutrophils was observed in the edematous subendothelial spaces. There were swelling and splitting of the internal elastic lamina. In the media, vacuolar change of the smooth muscle cells was evident and the cytoplasm showed a decreased staining property (Fig. 3). Severe edema was also seen diffusely or focally causing necrosis of the medial smooth muscle cells. In the adventitia or the perivascular area, a mild or moderate degree of inflammatory infiltration was found.

Degenerative and edematous changes in the media with mild to moderate inflammation in the intima and adventitia were the characteristic features of this type of lesion.

Type three (Necrotizing panarteritis)

Numerous inflammatory cells consisting of mainly lymphocytes, large mononuclear cells and neutrophils with scant eosinophiles were infiltrated

Fig.4. All layers of the arterial wall are extensively destroyed with numerous inflammatory infiltrations. Coronary artery. Case No.8 $\times 40$

Fig.5. Granulation tissue is formed in the intima and media. Fibrinoid material is seen along the luminal surface. Iliac artery. Case No.12 H & E $\times 100$

Fig.6. Thickening of the vascular wall by proliferation of fibrocytes and elastic fibers, scar tissue change, is marked. Fragmentation and splitting of the internal and external elastic laminae are evident. Iliac artery. Case No.32 Elastica van Gieson $\times 40$

Fig.7. Thickening and stenosis of a healed arteritis. Iliac artery. Case No.32 Elastica van Gieson $\times 14$

Fig.8. Aneurysm of the coronary artery. The lumen is completely occluded by a fresh thrombus. Coronary artery. Case No.5 H & E $\times 6$

rated in all layers of the vascular wall and were accompanied by a remarkable necrosis (Fig. 4). In the endothelial cells, there were extensive changes such as desquamation, degeneration or necrosis.

Splitting or fragmentation of the internal and external elastic laminae was visible in some parts and swelling and thickening in other parts. In the media, atrophy, degeneration or necrosis of the muscle cells was widely apparent among the marked inflammatory infiltrations.

Remarkable inflammatory infiltration was also observed in the perivascular area and was accompanied by proliferation and swelling of collagen fibers. Such necrotizing panarteritis involved particularly musculoelastic or middle sized arteries such as the iliac, main coronary, mesenteric or renal artery.

Type four (Granulation formation)

Proliferation of fibroblasts and capillaries accompanied by mild inflammatory cell infiltration mainly consisting of lymphocytes was observed. Fibrinoid material was occasionally present along the luminal surface or in the subendothelial space (Fig. 5).

Type five (Scar formation)

The intima and media were replaced by fibrous connective tissue losing their proper structures.

Inflammatory cells were scant in these parts. In the adventitia or perivascular area, proliferation of collagen and elastic fibers was prominent (Fig. 6). These changes were a sclerotic transformation of the arteritic lesion and showed features of healing. The vascular wall, in general, was thickened and the lumen was stenotic or occluded (Fig. 7). In addition to such severe sclerotic change involving the entire vascular wall, partial sclerotic fibrosis localized only in the intima, intima and media, or media and adventitia was frequently observed in many different arteries.

Type six (Aneurysm formation)

Extraordinary dilatation of the lumen and thinning of the vascular wall, aneurysm formation, were frequently present in the main coronary artery. Endothelial cells were extensively desquamated and thrombus was often observed occluding the lumen of such aneurysm (Fig. 8). The internal and external elastic laminae were stretched and fragmented.

Three laminar structures of the arterial wall, the intima, media and adventitia, were undistinguishable because of destruction and stretching of the vascular wall. The wall of the aneurysm itself also showed various changes according to the duration of the disease. In the patients who died within one month, the vascular wall showed mostly necrotizing panarteritis. In longer living

Fig.9. Minute thrombus is attached to a small vein the wall of which has a mild inflammatory infiltration, thrombophlebitis. Small vein in the thyroid capsule. Case No.1 H & E $\times 100$

patients, granulation tissue change replaced the acute inflammatory lesion. In cases of over two months duration, most of the vascular wall showed scar tissue change. In some patients, calcification was observed. Organization or recanalization of the thrombus formed in the aneurysm was also seen.

Aneurysm formation in the coronary artery was present in thirty-five out of thirty-seven patients. The cause of death of six patients with coronary aneurysm was rupture of the aneurysm. Aneurysm of the iliac artery was present in nine patients. One patient died following rupture of the iliac aneurysm with gross retroperitoneal hematoma. Aneurysm formation was rarely seen except in the main coronary and iliac arteries.

These six types of arteritic changes were not equally distributed throughout the entire arterial system. Severe lesion such as necrotizing panarteritis was usually localized in arteries such as the iliac, main coronary, mesenteric and renal arteries which directly branched from the aorta. Small sized arteries in the intraviscera usually showed degenerative change of the intima, lesion of type one, or edematous change of the media, lesion of type two. It was characteristic that these six types of lesion were simultaneously observed not

only in various areas of the arterial tree in the same patient, but also in different portions of one artery.

Inflammatory lesions were also observed in the venous as well as arterial system. Multiple thrombophlebitis was present in small veins in patients who died in the early phase of the disease (Fig. 9). Middle sized veins showed, in general, mild lymphocytic infiltration with edema in the media. Panphlebitis was also present in the larger veins such as the main coronary vein, vena cava inferior, vena portae or mesenteric vein in the patients who died within four weeks of onset (Fig. 10).

The phlebitis diminished gradually with duration of the disease, and a mild or moderate degree of phlebosclerotic change with proliferation of fibrocytes and collagen fibers was observed.

DISCUSSION

From general concept of pathomorphology on inflammatory development and its healing process⁹ it is evident that arterial changes in the five types of lesions, degeneration of the endothelial cells, edema and degeneration of the media, necrotizing panarteritis, granulation formation and scar formation, progress from the

Fig.10. Moderate inflammatory infiltration is seen in all layers of the vein. Note the degenerative and desquamation of the endothelial cells and edema of the media. Mesenteric vein. Case No.14 H & E $\times 200$

lesion of type one to that of type five. Therefore, these five types of lesions could be classified into five stages from the view point of morphogenesis of arteritis.

Vascular changes seen in a patient who died immediately after the onset can be regarded as the early lesion of arteritis. In the endothelial cells of the damaged artery in this patient, not only regressive changes such as degeneration, desquamation or necrosis, but also progressive changes such as hypertrophy or proliferation were observed.

The latter changes are considered to be the regeneration of the endothelial cells following injury. Directly beneath the area of the injured endothelial cells, the subendothelial space was edematous and the internal elastic lamina was swollen and acidophilic. Vacuolar change of the medial muscle cells and focal edema were also present in the media. From these findings, endothelial cell injuries seem to influence the various changes of the subendothelial space, internal elastic lamina and medial muscle layer under the damaged area. Electron microscopical observation on the small vessels in the skin of Kawasaki disease disclosed degeneration and necrosis of the endothelial cells with subendothelial edema, which preceded the changes of the medial muscle

cells.¹⁰ In spontaneously hypertensive rats,¹¹ we have already demonstrated that increased vascular permeability based on functional and/or structural changes of the endothelial cells induces changes in the medial muscle cells.^{12,13} In Kawasaki disease, particularly in the early stage of the arteritis, a similar process such as was seen in spontaneously hypertensive rats probably is work at in the development of the vascular changes.

Extraordinary thrombocytosis has been observed in hematological examinations¹⁴ and platelet adhesion or minute platelet thrombus was detected by the histopathology study herein. Extensive injury of the endothelial cells may play a role in aggregation or thrombogenesis of platelets at the damaged areas. A permeability facilitating agent such as serotonin probably takes part in acceleration of the edematous changes. Increased platelets may also play some role in the development of the proliferative change in arterial lesions. There are reports indicating that platelet factors stimulate the proliferation of fibroblast or arterial smooth muscle cells,^{15,16} and that intimal thickening is produced by the platelet aggregation.¹⁷

The drainage disturbance due to perivascular lymphangitis and phlebitis may accelerate the edematous change due to increased vascular

permeability from the intimal side. Tanaka et al.⁷ considered the lesion of vasa vasorum to be a causative factor in the arterial changes in Kawasaki angitis. From the above mentioned findings, it is considered that arteritic changes in Kawasaki disease develop with endothelial cell damage which causes edematous changes due to increased vascular permeability and drainage disturbance. Therefore, the primary lesion of the arteritis can be considered the stage of endothelial degeneration and increased vascular permeability.

Arkin¹⁸ divided the lesions of periarteritis nodosa into four stages. Alternative-degenerative change in the media was regarded as an initial change of periarteritis nodosa. In Kawasaki disease, it is considered that injuries of the endothelial cells precede the medial change. Thus, endothelial cell changes probably exist as the primary lesion in periarteritis nodosa. Arkin stated that "the endothelial changes are difficult to demonstrate, but we believe that they do occur".

The lesions of stage two to stage five in our classification approximately correspond to those of stage one to four in Arkin's classification.

Necrotizing panarteritis was observed particularly in the middle sized arteries which have an abundant small vessel network in their perivascular connective tissue, but was rarely observed in the small sized arteries in the intraviscera without such vessel network. Such a middle sized artery is prone to be attacked from both sides, from the intima with endoarteritis and the perivascular portion with periarteritis, by inflammatory invasion. These processes probably induce a florid vascular lesion in the entire vascular wall of the middle sized arteries.

When the destructive inflammatory attack exceeds the healing processes such as granulation and scar formation, dilatation of the vascular lumen, aneurysm formation, develops unable to resist the arterial blood pressure due to marked necrosis of the arterial wall.

Extensive splitting or fragmentation of the internal elastic lamina seems to be particularly important for the developmental mechanism of the aneurysm formation.

In the stage of scar formation, there were various degrees of sclerotic changes such as partial intimal thickening from a mild degree to total thickening and stenosis to a severe degree. This suggests that an arterial lesion of the first or second stage transforms directly to the healing process without passing through the florid lesion

such as panarteritis.

Various degrees of phlebitis were present in the venous system as well as in the arterial system. Phlebitis seems to appear in the early stage and disappeared soon after. It is apparent that in inflammatory invasion begins earlier and is temporary in the venous system, on the other hand, it starts later and persists longer in the arterial system. Therefore, the vascular lesions of Kawasaki disease should be termed systemic vasculitis rather than systemic arteritis.

Acknowledgements

Gratitude is due to our colleagues in the Department of Pathology, Kyoto University, Drs. K. Tasaka, H. Kubagawa, S. Ikehara, Y. Nakashima, S. Hirose, R. Kannagi, Y. Nakai and Y. Fujiwara, for collection of the specimens, to K. Tsuchida for photographic assistance and to M. Ohara for editing the manuscript.

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