Clinical and Pathological Studies of Five Autopsied Cases of Aortitis Syndrome

Part I. Findings of the Aorta and Its Branches, Peripheral Arteries and Pulmonary Arteries

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SUMMARY

The clinical findings and the necropsy reports of 5 cases with aortitis syndrome are described. All cases had extensive type of chronic arteritis (aortitis syndrome). The fact that in some cases of aortitis syndrome the lesions of the aorta and its main arteries could extend to the peripheral arteries was noted. The pathological changes of the wall of vasa vasorum were found to correspond to those of the medial and adventitial area of the aorta and pulmonary artery in distribution. The marked similarity between the aortic and pulmonary arterial lesions suggest the common pathogenesis for both lesions.

Additional Indexing Words:

Aortitis syndrome	Aorta and its branches	Peripheral arteries
Pulmonary arteries	Aortic insufficiency	Hypertension
vasorum		Vasa

AORTITIS syndrome caused by arteritis of the aorta and its major branches, reveals various clinical findings, such as Takayasu's ocular fundi, pulseless disease, atypical coarctation of the aorta, renovascular hypertension, aortic insufficiency, arterial aneurysm and pulmonary artery lesion. These findings are attributed to narrowing, occlusion or dilatation of the aorta, major arteries and pulmonary arteries.

The present study deals with clinical and pathological observations based on the records of 5 autopsied cases of aortitis syndrome, experienced at the Second Department of Internal Medicine, University of Tokyo, from March, 1951 to September, 1970. In this paper, are described mainly the clinico-pathological problems of vascular system in aortitis syndrome.

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CASE REPORTS

Case 1. Y. Y., a 28-year-old male, was admitted to the Tokyo University Hospital, complaining of nausea, vomiting, palpitation and edema on April 11, 1956. Dyspnea on exertion, general malaise, diarrhea and edema appeared at age of 16. The patient developed right coxalgia and myalgia of the feet, with recurrence in the winter at age of 18. In 1954, he developed congestive heart failure. At that time vertigo provoked by turning the head backward was noted. In February, 1956, he had frequent attacks of nocturnal dyspnea.

Physical examination revealed puffy face and edema on the lower extremities. Dilatation of the jugular vein was noted. Pulsation of the radial arteries was weak on both sides. Pulse was regular with a rate of 104. Systolic blood pressure was 180 mm. Hg in the right arm and 104 mm. Hg in the left. The heart was enlarged bilaterally on percussion. Apical impulse was seen on the anterior axillary line. On auscultation, besides vascular murmur of the neck, there was systolic murmur at pulmonic area, and apical rumbling and basal blowing diastolic murmurs were audible. The liver with hard margin and tenderness was palpable about 2 finger-breadths below the right costal margin.

The patient was treated with digitalis, but he expired by an accident on May 10, 1956.

Case 2. C. K., a 23-year-old female, was hospitalized under a diagnosis of juvenile hypertension. Three years prior to admission, the patient began to complain of headache, nausea and visual disturbance. At the time of admission blood pressure was 260/98 mm. Hg in the right arm and 260/126 mm. Hg in the left. Ophthalmoscopy exhibited marked arteriosclerosis of the retinae and right retinal hemorrhage. White blood cell count was 14,200 and C-reactive protein was negative. In the evening on the day of admission, the patient developed numbness of the upper and lower extremities of the right side, headache and nausea followed by loss of consciousness, and died in early morning on the next day.

Case 3. R. A., a 32-year-old female, was admitted to hospital complaining of decreased muscle strength of the extremities and difficulty in swallowing on September 17, 1965. Her illness started 2 months before with tiredness of the both legs. Subsequently, she had also weakness of the both hands and muscle strength of the both extremities gradually decreased, followed by difficult swallowing without sensory disturbance. She had history of tuberculosis at age of 19 and she experienced pneumonia and tonsillitis several times. However, weak radial pulse was noted at age of about 14.

Physical examination revealed slightly edematous and anemic face. Her pulse was 110 per min., regular. Respiratory rate was 30 per min. She was febrile (fluctuating fever from 37°C to 38°C). All the arterial pulses were well palpable except the left radial arterial pulse. Blood pressure was 120/70 in the right arm. Moist rales were audible over the middle and lower areas of the right lung field. Cardiac enlargement was not recognized. She had prominent muscle atrophy of the lower extremities and a part of the upper extremities.

A tentative diagnosis of polyneuritis with pneumonia was made. While blood cell count was 12,000 with neutrophils 76% and erythrocyte sedimentation rate was 49 mm. at 1 hour. The abnormal laboratory data were as follows: S-GOT 288 units/ml., S-GPT 288 units/ml., ZnTT 16. ECG exhibited ST-T abnormality and

peculiar Q, suggesting myocardial damage.

During the period of investigation, she was treated with antibiotics, ACTH and multivitamins, without apparent effect. She had progressive muscular weakness in spite of the treatment above described.

On September 27, she developed sudden apnea and expired shortly afterwards.

Case 4. T. O., a 56-year-old female, was admitted to hospital on January 20, 1961, complaining of dull pain on the right temple, attacks of palpitation, shortness of breath and tachycardia, for about one and a half years. These symptoms appeared on exertion and were relieved by rest. At the age of 33, when operated upon for retroverted uterus, she was noted her radial pulse to be very feeble. About a year ago, she experienced an episode that her right leg suddenly became dark red without pain and intermittent claudication for a few hours.

Outstanding physical findings on the first admission were as follows: blood pressure was 240/50 mm.Hg in the right arm, 130/70 mm.Hg in the left and 180/70 mm.Hg in the legs. Both carotid arteries were strongly pulsating, with systolic thrill and bruit. The cardiac dullness was enlarged and a loud systolic murmur was heard over the manubrium sterni. Atrial gallop and paradoxical splitting of the second heart sound were also noted. A faint diastolic murmur was noted at the Erb's area. A harsh systolic bruit with slight thrill was present around the umbilicus, and on the back.

Retrograde aortography revealed a lesion of aortic arch type, there was an abrupt fall in blood pressure at the level of the diaphragm, together with systolic bruit heard about the umbilicus, suggesting narrowing of the abdominal aorta. This evidence indicates extensive type of aortitis syndrome.

On the next admission in June, 1967, she had an exertional dyspnea and generalized edema. She was treated with digitalis and diuretics, and these symptoms were abolished.

A few weeks afterwards, palpitation and dyspnea appeared again. She was admitted to another hospital in October of the same year. On admission physical examination revealed tachycardia (180 per min., irregular), marked cardiomegaly with liver swelling and severe pretibial edema. Blood pressure was 160/60 mm.Hg in the right arm and 110/? mm.Hg in the left. Digitalis and diuretics were of only temporary effect. On December 17, 1967, stridor, hemoptysis and cyanosis appeared followed by Cheyne-Stokes' respiration. Sudden death occurred 2 days later.

Case 5. M. Y., a 34-year-old female, was admitted to hospital, with a history of dullness in the legs, intractable anemia and hypertension of 1 year's duration. Her illness started in 1953 with exertional dullness in the lower extremities, followed 5 months later by hypochromic anemia, which did not respond to iron drug therapy for 2 months. Since then, she was found to have hypertension. On her first admission in 1954, blood pressure was 194/84 mm.Hg in the right arm, 192/60 mm.Hg in the left, and 146/110 mm.Hg in the both lower extremities. She was discharged without apparent improvement.

After discharge, the patient experienced attacks of cerebral ischemia lasting for 5 min. On her next admission in 1958, she had advanced anemia with complaints of headache and palpitation. Administration of steroid hormone resulted in improvement of anemia and accentuated erythrocyte sedimentation rate from 163 mm. to 53 mm. in 1 hour. However, high blood pressure and the above symptoms persisted. After her marriage in 1960, she developed hypertension (250/? mm.Hg)

during pregnancy, and forceps delivery was performed in 1961.

On the third admission in 1963, she complained of anginal attacks and exertional palpitation lasting for 5 months. She was febrile (37.5°C), tachycardic (92 per min.) and anemic. Blood pressure was 202/90 in the right arm, 200/80 in the left, and 170/70 in the both lower extremities. There was cardiomegaly with an ejection systolic murmur at the base. A systolic bruit was heard at the base of the neck on both sides and in the epigastrium. The second heart sound was intensive and a diastolic murmur was audible at the Erb's area. Pulmonary and abdominal areas revealed nothing particular.

A diagnosis of extensive type of aortitis syndrome with aortic insufficiency was made by aortography. She was treated with prednisolone and other drugs, and was discharged in a good condition. After second delivery in 1968, transient dyspnea was experienced, but, after then the patient was apparently healthy. On May 27, 1969, she died suddenly.

Various investigations of the 5 cases are summarized in Table I.

RESULTS

(1) Clinical Findings

Clinical review of the present series exhibited glomerulonephritis, pulmonary tuberculosis and pneumonia in the past history. Main symptoms were headache, vertigo and palpitation. Weak or absent pulsation of the left radial artery was noted in 3 cases. Hypertension was detected in the upper extremity

Table I. Laboratory Data

			Case 1	Case 2	Case 3	Case 4	Case 5
Erythrocyte sedimentation rate (mm. in 1st hour)			2		63	63	73
White blood cell count			5,700	14,200	12,000	12,000	9,900
C-reactive protein			1(+)	(-)	(-)	6(+)	>6(+)
Anti-aorta antibody						5	40
Serum cholesterol (mg./100 ml.)			225		116	233	250
ECG	Left ventricular hypertrophy			+		+	+
	ST-T abnormalities				+	+	+
Chest X-ray film	Cardiac enlargement		+	+		+	+
	Dilatation of ascending aorta		+			+	+
	Calcification of aorta	ascending				+	
		arch	+			+	+
		descending	+				
Aortography						Extensive type	

in 3 cases and in the lower extremities in 2 cases. Aortic and mitral regurgitant murmur was audible in 3 and 1, respectively.

There were 3 cases with accelerated erythrocyte sedimentation rate, 4 with leukocytosis, 3 with positive C-reactive protein and one with anti-aorta antibody of a high titer (Table I). ECG showed left ventricular hypertrophy, ST-T abnormalities and chest X-ray film revealed cardiac enlargement, dilatation of the ascending aorta and calcification of the aorta. Two cases (Cases 4 and 5) examined with aortography had extensive type of aortitis syndrome with aortic insufficiency, and one of them (Case 5) had renal arterial stenosis.

Clinical diagnosis in these 5 cases was combined valvular disease in 1 case (Case 1), juvenile malignant hypertension in 1 (Case 2), polymyositis in 1 (Case 3), and extensive type of aortitis syndrome in 2 (Cases 4 and 5). Their cause of death was cardiac failure, cerebral hemorrhage and paralysis of respiratory muscle (Table II).

Table II. Clinical Diagnosis and Cause of Death

	Case 1	Case 2	Case 3	Case 4	Case 5
Clinical diagnosis	Aortic and mitral insufficiency	Malignant hypertension	Polymyositis	Aortitis syndrome	
Cause of death	Accident (heart failure)	Cerebral hemorrhage	Respiratory muscle paralysis	Heart failure	

(2) Pathological Finding*

All cases included in this report had extensive type of chronic arteritis (Table III). Case 3 had an anomaly where the right subclavian artery arose from the aortic arch, and Case 4 had an anastomosis between the superior and the inferior mesenteric arteries.

Looking through the aorta itself, descending thoracic and abdominal aortae gave grossly more severe changes with atheroma, calcification and ulceration than the aortic arch (Fig. 1). In the trunks of the aortic arch, adventitial fibrosis and intimal thickening were more marked than in the aortic arch itself, resulting in narrowing or obstruction of these vessels. Such lesions of the left subclavian artery were found in all cases. The same lesions were also observed in the main arteries arising from the abdominal aorta. Bilateral renal artery narrowing was marked in 4 cases.

In Case 4, complete obstruction of the left subclavian artery was noted by gross examination (Fig. 2). Histopathologically, cell infiltration was seen in an islet pattern, and fibrosis and fragmentation of elastic fiber were marked

* Cardiac, coronary artery, and aortic valvular findings will be reported elsewhere.

Table III. Lesions of the Aorta and Its Main Branches

	Case 1	Case 2	Case 3	Case 4	Case 5
Ascending aorta	⊖ A C	F		⊖ CI F	⊖ A C
Aortic arch	A C	F		⊖ CI A	A C
Common carotid artery		F		O CI	
right		F			
left	O A C	F		O CI	
Subclavian artery		F	(*)	● CI A	
right		F			
left	●	O CI F	O CI	● CI F	O
Brachiocephalic artery	O A C	F		CI	O
(Left axillary artery)			O CI	O CI F	
(Left brachial artery)					
Descending thoracic aorta	CI A C F		F	C UI	O A C F
Abdominal aorta	A C	CI A F	A F	A C UI F	O CI C F
Superior mesenteric artery		O		O } anastomosis big	O CI
Inferior mesenteric artery					
Celiac artery	O F			O	O
Renal artery		O CI	O	A	O CI
right	O	O CI	O		
left	O	O CI	O	A	O CI
(Left common iliac artery)				CI	F

CI : Cell infiltration
F : Fragmentation of elastic fiber

UI : Ulceration
⊖ : Dilatation

O : Narrowing
C : Calcification

● : Obstruction
A : Atheroma
(*) arising from aortic arch

Fig. 1. Case 5. The cut section of the ascending aorta, aortic arch, descending thoracic aorta (middle and diaphragmatic level), abdominal aorta and both renal arteries. Descending thoracic and abdominal aortae show atheroma and calcification with marked narrowing.

Fig. 2. Case 4. The cut section of the brachiocephalic, left common carotid (narrowing) and left subclavian (complete obstruction) arteries showing the marked adventitial thickening.

in the media. Cell infiltration around the vasa vasorum and fibrosis were also marked in the adventitia (Figs. 3 and 4).

The above described findings were noted from the initial portion of the left subclavian artery to the axillary artery continuously (Fig. 5). In addition,

Fig. 3. Case 4. Cell infiltration in an islet pattern and fibrosis in the media of left subclavian artery (Haematoxylin and eosin, $\times 100$).

Fig. 4. Case 4. Cell infiltration around the vasa vasorum in the adventitia of left subclavian artery (Haematoxylin and eosin, $\times 100$).

Fig. 5. Case 4. Adventitial cell infiltration and medial hyalinoid degeneration in the left axillary artery (Haematoxylin and eosin, $\times 100$).

this case had the similar changes in the left common iliac artery (Fig. 6). Such peripheral arterial changes were similar to those in the aorta and the main branches also in Cases 3 and 5.

In vasa vasorum, intimal proliferative thickening and perivascular cell infiltration were characteristic, and distribution of these changes coincided with that of the medial and adventitial change of the aorta and main pulmonary artery such as diffuse fibrosis and cell infiltration. Narrowing of the walls of

vasa vasorum was noted in association with these adventitial changes (Fig. 7).

In the pulmonary artery, from its initial portion to the hile of the both lungs, adventitial fibrosis and intimal thickening were noted, showing changes similar to those in the aorta and its main branches (Fig. 8).

Fig. 6. Case 4. Medial elastolysis and adventitial cell infiltration in the left common iliac artery (Haematoxylin and eosin, $\times 50$).

Fig. 7. Case 3. Two vasa vasorum in the abdominal aorta showing obstruction and narrowing (Haematoxylin and eosin, $\times 200$).

Fig. 8. Case 5. The upper larger artery shows ascending aorta and 2 of the lower arteries show narrowed main trunks of pulmonary artery.

Arteriosclerotic change was scarcely found and cell infiltration was distributed in a nodular pattern in the trunk and its main branches (Fig. 9). Other changes including fragmentation or proliferation of elastic fiber and fibrosis were noted in Case 5 (Table IV). No significant changes were observed in the lung tissues.

Fig. 9. Case 5. Cell infiltration in the media of main trunk of pulmonary artery (Haematoxylin and eosin, $\times 100$).

Table IV. Pulmonary Arterial and Pulmonary Tissue Lesions

		Case 1	Case 2	Case 3	Case 4	Case 5
Pulmonary artery	Narrowing of lumen	—	—	—	—	+(T)
	Arteriosclerosis	—	—	—	±	—
	Thrombus	—	—	—	—	—
	Thickening	±	—	+	—	+
	Cell infiltration	—	—	±	—	±(B)
		—	—	—	—	+(T), ±(B)
	Elastic fiber	—	—	—	—	+(B)
		—	—	—	—	+(T)
	Adventitial fibrosis	—	—	+	—	+(T)
Lung	Neovascularization	—	—	—	—	+(B)
	Weight (left, right) (Gm.)	360, 470	180, 210	470, 500	370, 890	330, 330
	Pneumonia	+	—	±	—	+
	Congestion	±	—	—	—	+
	Bleeding	—	+(pleural)	—	—	+
	Fibrosis	+	—	—	+(pleural)	—

T: Trunks of pulmonary artery

B: Branches of pulmonary arteries

Table V. Autopsied Cases of Aortitis Syndrome with Peripheral Arterial Lesion in Literature

Year	Reporter	Age and Sex	Type	Ope.	Death	(SA)			AA			BA			CIA			IIA			EIA			FA			TA
						l.	r.		l.	r.		l.	r.		l.	r.		l.	r.		l.	r.		l.	r.		l.
1940	Ohta ¹⁾	25, Female	Extensive		+			○			○			○													
1951	Tamura ²⁾	28, Female	Arch		+			●						●													
1952	Morishima et al. ³⁾	27, Male	Arch		+	○		○	○		○	○		○													
1955	Nagashima et al. ⁴⁾	27, Female	Arch	+				○						○													
1956	Ask-Upmark et al. ⁵⁾	40, Female	Arch		+												○										
1958	Murakami et al. ⁶⁾	23, Female	Arch		+	○		○				○		○													
1960	Kimoto et al. ⁷⁾	29, Female	Arch	+		●						●															
1964	Grollman et al. ⁸⁾	43, Female	Arch		+												○					○					
		34, Female	Extensive	+																							
1967	Gotman et al. ⁹⁾	33, Female	Extensive		+																		○				
		27, Female	Extensive		+																			○			●

● : Obstruction

○ : Narrowing

◎ : Aneurysm

SA : Subclavian artery

AA : Axillary artery

BA : Brachial artery

CIA : Common iliac artery

IIA : Internal iliac artery

EIA : External iliac artery

FA : Femoral artery

PA : Popliteal artery

TA : Tibial artery

l : Left

r : Right

Table VI. Autopsied Cases of Aortitis Syndrome with Pulmonary Arterial Lesion in Literature

Year	Reporter	Age and Sex	Type	Lumen	Thickening		FE	CI	Others
					Media	Adventitia			
1940	Ohta ¹⁾	25, Female	Extensive	○	+	+			
	Kawai et al. ¹⁵⁾	24, Male	Arch	○	+	+		+	
1951	Ueda et al. ¹⁶⁾	20, Female	Arch	●				+	
1956	Ask-Upmark et al. ⁵⁾	40, Female	Extensive						Lipoid sedimentation
1958	Murakami et al. ⁶⁾	23, Female	Extensive	○	+	+		+	
1961	Takeda et al. ¹⁷⁾	30, Female	Arch						Granuloma (media)
1963	Nasu ¹⁴⁾	10, Female	Extensive	○ or ●					Small arterial lesion
		18, Female							
		19, Female							
		20, Female							
		25, Female							
		26, Female							
		27, Female							
		28, Female							
		30, Female							
		5, Male							
		24, Male	Arch						Small arterial lesion

● : Obstruction ○ : Narrowing FE : Fragmentation of elastic fiber CI : Cell infiltration

DISCUSSION

All cases reported in this paper had wide spread chronic arteritis, distributed in the aorta and its main branches, that is, extensive type of aortitis syndrome.

The findings in Case 4, however, suggest the possibility of the development of the similar lesion in the middle-sized arteries. Autopsy cases of this disease with peripheral arterial involvement have been not infrequently reported, but they have been studied not sufficiently (Table V).¹⁾⁻⁹⁾ The question naturally arises whether these changes occur as the extension of aortitis itself, or they occur from the secondary changes or from the other combined disease. This requires confirmation by further necropsy studies.

Our cases showed that narrowing or obstruction of vasa vasorum was found mostly in the areas corresponding to adventitial fibrosis and/or cell infiltration of the aorta and main pulmonary artery. It is, in general, accepted that the change of vasa vasorum is one of the most important factors in the development of aortitis syndrome (Marinesco,¹⁰⁾ Ohta,¹⁾ Frøvig,¹¹⁾ Correa,¹²⁾ Danaraj¹³⁾ and Nasu¹⁴⁾).

Although pulmonary artery lesions are found in a considerable number of cases, they were rarely related to the clinical symptoms. Active stage of typical pulmonary arteritis is very rarely noticed pathologically in this disease (Table VI).^{1), 5), 6), 14)-17)} In Case 4 of our series, there was the picture of active, diffuse pulmonary artery inflammation which was very similar to aortic lesion. From the findings obtained at necropsy in the present case we are of opinion that the common casual relationship between the two lesions is conceivable. However, the time relationship between the both lesions is obscure, that is, it is unknown whether the change in the pulmonary artery may indicate primary inflammatory process or the secondary involvement from the contiguous severely diseased aorta.

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REFERENCES

1. Ohta, K.: *Trans. Soc. Path. Jap.* **30**: 680, 1940.
2. Tamura, J.: *Trans. Soc. Path. Jap.* **40**: 192, 1951 (in Japanese).
3. Morishima, M. and Nakamura, T.: *Trans. Soc. Path. Jap.* **40**: 224, 1952 (in Japanese).

4. Nagashima, M. and Nakazato, Y.: J. Jap. Soc. Int. Med. **43**: 901, 1955 (in Japanese).
5. Ask-Upmark, E. and Fajers, C. M.: Acta med. Scandinav. **155**: 275, 1956.
6. Murakami, S., Yamada, M., Tsuda, K., and Ohsawa, K.: J. Jap. Soc. Int. Med. **47**: 703, 1958 (in Japanese).
7. Kimoto, S.: Surg. Diag. & Treat. (Clinical Conference) **2**: 907, 1960 (in Japanese).
8. Grollman, J. H. and Hanafec, W.: Radiology **83**: 387, 1964.
9. Gotsman, M. S., Beck, W., and Schrire, K.: Radiology **88**: 232, 1967.
10. Marinesco, G. and Kreindler, A.: Presse Méd. **44**: 833, 1936.
11. Frøvig, A. G. and Löken, A. C.: Acta psychiat. et neurol. Scandinav. **26**: 313, 1951.
12. Correa, P. and Ajanjo, J.: Am. J. Clin. Path. **29**: 560, 1958.
13. Danaraj, T. J. and Ong, W. H.: Circulation **20**: 856, 1959.
14. Nasu, T.: Angiology **14**: 225, 1963.
15. Kawai, N., Kawai, K., and Tashiro, K.: Trans. Soc. Path. Jap. **40**: 190, 1951 (in Japanese).
16. Ueda, M., et al.: J. Med. Hyogo Univ. **2**: 10, 1951 (in Japanese).
17. Takeda, F., Ohneda, G., Suto, K., Suto, H., and Kubota, K.: Gumma J. Med. Sci. **10**: 27 1961.