Acta Pathol. Jpn. 34(4) : 797~811, 1984

PROGERIA WITH CARDIAC HYPERTROPHY AND REVIEW OF 12 AUTOPSY CASES IN THE LITERATURE

Takeshi SHOZAWA, Masato SAGESHIMA, and Eikichi OKADA

Second Department of Pathology, Akita University, School of Medicine, Akita

An autopsy of an 11 years 5 months old boy with progeria is presented. Hyaluronuria, low growth rate of skin fibroblasts, decreased number of T-cells in lymphocyte subpopulation, increase of anti DNA antibody, and antibody for microsome of thyroid gland were detected clinically. He had suffered an attack of cerebral infarct and died of congestive cardiac failure. Pathologic findings were scleroderma-like skin atrophy, moderate arteriosclerosis of the aorta and great arteries, severely narrowed coronary sclerosis with an extensive subendocardial fibrosis, a large left cerebral infarct with pin-holed stenosis of both internal carotid arteries, cortical atrophy of thymus, and atrophic lymph nodes. The cardiac muscle fibers were slightly hypertrophied and measured 15.5±2.8 μ in diameter. Histologic findings suggest that increasing of collagen in the connective tissue may play an important role in progeria. Further study of metabolic disturbance in the connective tissue of progeria is necessary. ACTA PATHOL. JPN. 34 : 797~811, 1984.

Progeria (Hutchinson-Gilford syndrome) is a rare disorder of children, characterized by arrested growth and premature senility.[4] The etiology is still obscure. Since the first description by GILFORD[6] in 1904, only twelve autopsy cases[1,5,11,13~15,19,21,24,27] have been reported. This report presents an autopsy case of an 11 years 5 months old boy died of cerebral infarct and congestive cardiac failure. The first clinical report about this patient has been described by TOKUNAGA *et al*[28] in 1978 and the second by SHIMADA *et al.*[25] in 1982.

Case Report

The patient was an 11 years 5 months old Japanese boy. Both parents and his elder brother were healthy. He was a full-term baby, weighing 2,650 g. The skin over the abdomen and legs was somewhat discolored at birth. After 1 month of age, elasticity of the skin began to loosen and at 2 months of age, the lower half of the body became edematous. At 4 months of age, he was brought to the Tohoku Universtiy Hospital. He weighed 5,600 g. However, physical development was retarded and the

Accepted for publication August 27, 1983.

所澤 剛, 提嶋 眞人, 岡田 英吉

Mailing address : Takeshi SHOZAWA M.D., The Second Department of Pathology, Akita University, School of Medicine, 1-1 Hondo, Akita 010, JAPAN.

skin biopsy was compatible with those of diffuse scleroderma. Thus he was diagnosed as progeria. After 1 year and 4 months of age, senile appearance became apparent and he began to lose his hair. At the age of 9 years, hyaluronuria was detected by Dr. TOKUNAGA. Five months before his death dysesthesia of the right upper extermity, dysarthria, and dysphagia appeared suddenly and he was sent to the Akita University Hospital. Physical examination and an examination of the brain by computer tomography revealed left cerebral infarct. Fibrinolytic and anticoagulant therapy was done immediately, but no improvement was obtained. Cardiac dialation (CTR 0. 62), marked congestion and abnormal wave of ECC suggested congestive cardiac failure and myocardial damages. In spite of digitalization the congestive cardiac failure did not improve and edema appeared in his feet. He died suddenly. Clinically, hyperlipemia of Type IV (WHO) was detected and culture of the skin fibroblasts showed a low growth rate and short life-span. T-cells were decreased to 25.6% in lymphocyte subpopulation, anti DNA antibody and antibody for microsome of thyroid gland were increased up to 14.5 u/ml (normal 10 u/ml) and 400X, (normal. 100 X), respectively.

Fig. 1. Photograph of the patient after death. Markedly emaciated boy. Small face with micrognathia, beak-like nose, absence of eyebrows, and sparsity of eyelashes. Short clavicles and bulged joints of all extermities.

Autopsy was performed 5 hours after death. His height was 104 cm and the body weighed 12 kg. The face was characterized with micrognathia, beak-like nose, absence of eyebrows and sparsity of eyelashes. The hair was almost absent and the scalp was taut and thin with prominent vein. Fontanelle were closed. The skin over the chest and abdomen was atrophic and had a mottled dark brown pigmentation. Subcutaneous fat tissue was minimal throughout the body. The joints of all the extermities bulged and the muscles were markedly atrophied. The nails of both thumbs and all toes were not grown. Double teeth of incisor of the lower jaw were observed. Both pleural and pericardial cavities contained less than 5 ml of serous fluid (Fig. 1).

The heart weighed 200 g. The left ventricle dilated markedly and the right moderately. The lateral wall of the left ventricle measured 0.8 cm and the right 0.3 cm in thickness. Spotty bleedings were seen in subepicardial layer of the left apex. An old irregular subendocardial scar was located in the anteroseptal region of the lower 2/3 of the left ventricle, extending into the lateral wall and spreading circularlly in the apex. No mural thrombi adhered to the endocardium of the left ventricle

(Fig. 1). Microscopical examination of the lesion revealed a laminal replacement of muscle fibers by fibrous tissue involving the inner half of the ventricular myocardium, partially extending into the outer layer. There were numerous dilated small arteries and sinusoid like veins in the lesion. Scattered islands of fibrosis of all stages were seen in the outside muscle layer of the laminal scar and no polymorphonuclear leucocytes were infiltrated in these foci. There were a few small calcium deposits in the scar. Most of the muscle fibers survived in the most inner layer of the anteroseptal region were hydropic (Fig. 3). Cardiac muscle fibers contained a few lipofuscin pigments in the perinuclear halo. The average diameter of the cardiac muscle fiber was $15.5 \pm 2.8\,\mu$, the average length of the nucleus $17.9 \pm 3.8\,\mu$, and the frequency of binucleated myocardial cells 5.4%.

Distribution of 3 coronary artery branches was right predominant. Severely narrowed arteriosclerosis was found in the main branches by 3 mm step cross sections. The left anterior descending artery was most severely involved and the degree of the luminal stenosis was estimated to be nearly occluded, 75% and 90% in the left anterior descending, left circumflexus and right coronary artery, respectively. Histological sections of the coronary arteries disclosed severe fibrous intimal thickening with fatty droplets, calcium, and foam cells lying beneath the endothelium. The subintimal layer was replaced with collagen and the smooth muscles were atrophic in the media. There was no thrombi in the coronary arterial lumen (Fig. 4). Small subepicardial

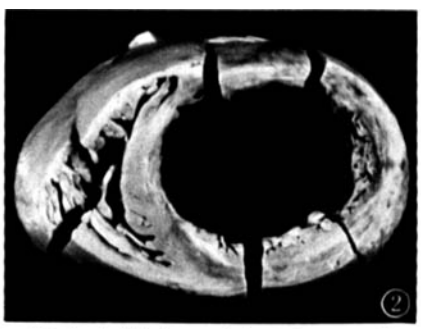


Fig. 2. Marked dilation of the left ventricle with extensive subendocardial fibrosis of anterolateral wall.

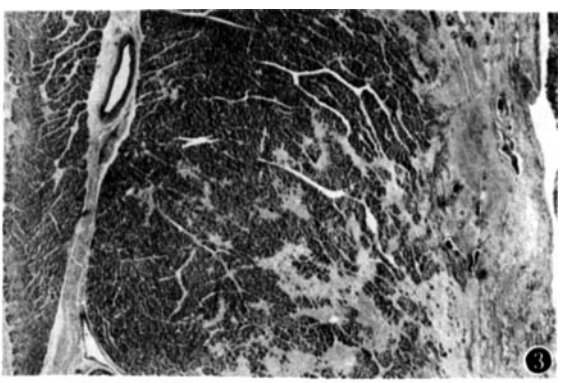


Fig. 3. Wide-spread subendocardial fibrosis of the anterior wall with congestion in sinusoid-like veins. Note scattered small foci of fibrosis in the middle layer. Elastica Masson Trichrome (El. M.T.), × 4.

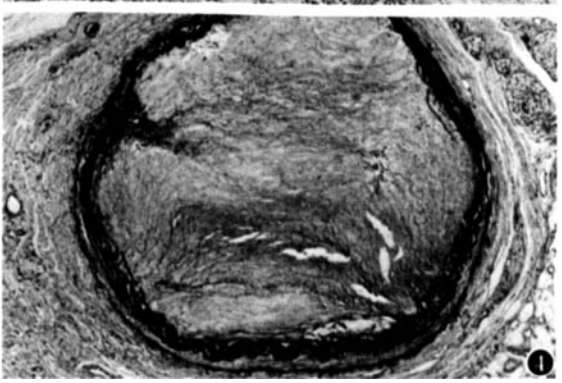


Fig. 4. Transverse section (TS) of the left anterior descending artery with eccentric narrow slit lumen. Stenosis due to fibrous thickening and calcificaon of the intima. El. M.T., × 12.

and intramyocardial branches of the coronary arteries were patent and showed minimal arteriosclerosis. In the adventitia of the coronary artery and connective tissue of the epicardium, an increase of collagen was observed.

Both SA and AV nodes were well developed. No particular pathological changes were found in the conducting system for the cause of sudden death by microscopic study of step serial sections. The circumference of the valve rings were as follows; aortic, 3.5 cm, mitral, 5.5 cm, pulmonary, 4.8 cm and tricuspid, 7.5 cm. The valve cusps and the chorda tendinae were smooth and delicate.

The aorta was moderately atherosclerotic with scattered atheromatous plaques in the abdominal segment. The abdominal aorta was quite stiff and showed markedly fibrous intimal thickening with atheromatous degeneration in the lower half of the intima and calcification histologically. Elastic membranes were well preserved in the media. However, smooth muscles of the most inner layer of the media were degenerated and replaced with collagenous tissue (Fig. 5). Both of the carotid sinus revealed severe fibrous thickening of the intima with calcification, The proximal segment of superior mesenteric, renal artery, and splenic artery stem showed similar changes to the coronary artery accompanied with stenosis up to 75%, 50%, and 50%, respectively (Fig. 6a). The left femoral artery was patent and the intima was almost smooth, while the media was replaced with collagen and the smooth muscles were atrophic. Intimal thickening was also seen in small arteries of the submandibular gland (Fig. 6b) and periarticular region of the left knee (Fig.6c). Central arteries of the spleen were hyalinized. Small arteries and arterioles of other organs such as liver, pancreas, adrenals, and gastrointestinal tracts were patent and free of the disease.

The brain weighed 1,190 g. Both internal carotid arteries at the level of siphon showed a severe degree of arteriosclerosis with pin-point narrowed lumen (Fig. 6d). The left parietotemporal area supplied by the middle cerebral artery was friable and soft. On the cut-surface there were severe congestion of the vessels and in the left parietotemporal region a $3.5 \times 4 \times 5$ cm sized old cerebral infarct (Fig. 7). Microscopical examination of the lesion revealed proliferation of hypertrophied astrocytes and macrophages contained fatty droplets. Other sections of the brain, including the

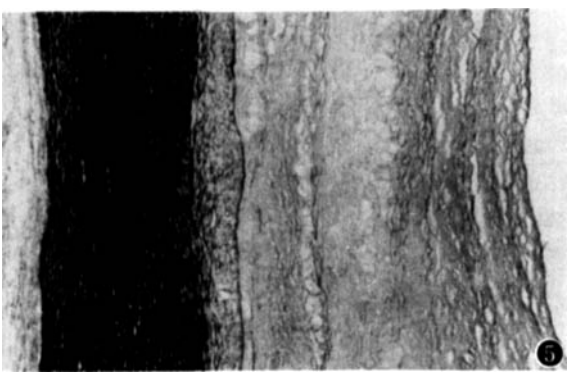


Fig. 5. Marked fibrous thickening of the intima of the abdominal aorta with atheromatous degeneration in the lower half. Increasing of collagen in the most inner layer of the media and well preserved elastic membrane. El. M.T., × 12.

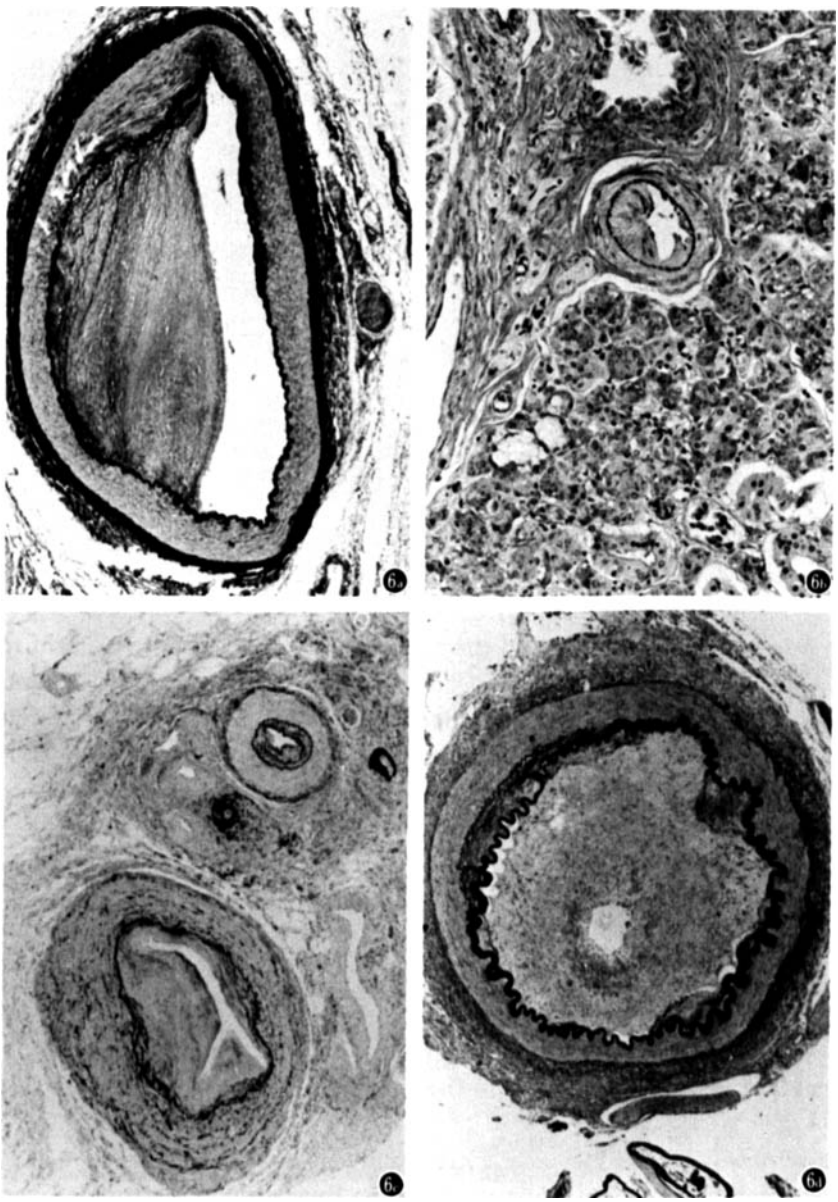
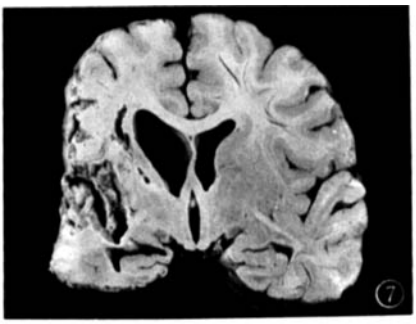


Fig. 6a. TS of stem of spleen artery with 50% stenosis due to an eccentric intimal thickening. El.M.T., × 10. 6b. TS of small artery with eccentric elongated lumen in the submandibular gland. Stenosis due to an eccentric fibrous thickening of the intima. El. M.T., × 50. 6c. TS of two small arteries in periarticular region of the left knee. The larger artery with eccentric elongated and the smaller one with almost central circular lumen. Stenosis due to fibrous intimal thickening. Marked thickening of the media in the latter. 6d. TS of the left internal carotid artery at the level of siphon with central small lumen nearly occluded due to marked fibrous intimal thickening. El. M.T., × 10.



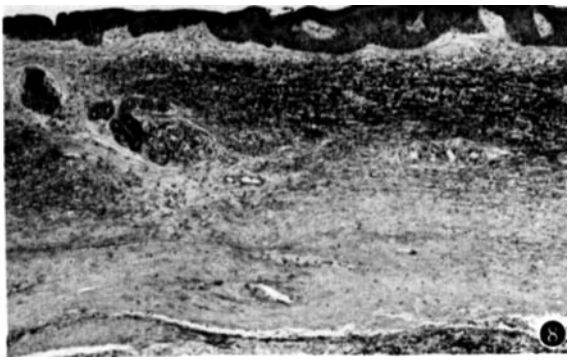


Fig. 7. Large old cerebral infarct of the left parietotemporal region supplied by left middle cerebral artery.

Fig. 8. Skin of chest wall. Thin epidermis, proliferation of elastic fibers in the upper dermis and of collagen in the lower. El. M.T., × 12.

brain stem and cerebellum were within normal limits and no accumulation of lipofuscin was seen in nerve cells by H.E. stain.

The left lung weighed 95 g and the right 125 g. Lower part of the right lower lobe was atelectatic. The other lobes were congested and accompanied with spotty bleedings. Scattered foci of hemosiderin laden macrophages were also noted on the histologic sections. Pulmonary arteries appeared free from arteriosclerosis.

The skin from the chest wall was examined histologically. Epidermis was rather thin and the number of melanin pigments were increased in the basal epithelial layer. Elastic fiber was proliferated and irregular in the upper dermis. In contrast collagen was proliferated in the lower half of the dermis. Sweat glands, sebaceous glands, and hair follicles were reduced in number. There was a slight amount of subcutaneous fat (Fig. 8).

The lefs kidney weighed 90 g and the right 80 g. The renal cortex was anemic, while the medulla was congested. No particular pathological changes were observed in the kidney. Submucosal connective tissue of the urinary bladder was thicker than usual.

The liver weighed 440 g and was congested. The gallbladder was edematous and contained thick bile. Microscopic study of the liver disclosed atrophic liver cell cord with fatty droplets and thicker fibrous tissue in Glisson's sheath and liver vein wall than would be expected in a child of this age (Fig. 9a).

The gastrointestinal tract was intact with the exception of increased collagen fiber bundles in the submucosal connective tissue (Fig. 9b).

The pancreas weighed 29.8 g. Periductar and interacinar fibrosis was prominent and small inslets were increased slightly in number (Fig. 9c). Similar fibrosis was observed in the submandibular glands, some acini were atrophic, and ductuli contained secretory material, which was calcified partially.

The thymus weighed 3.6 g and was thin. The cortex was markedly atrophic,

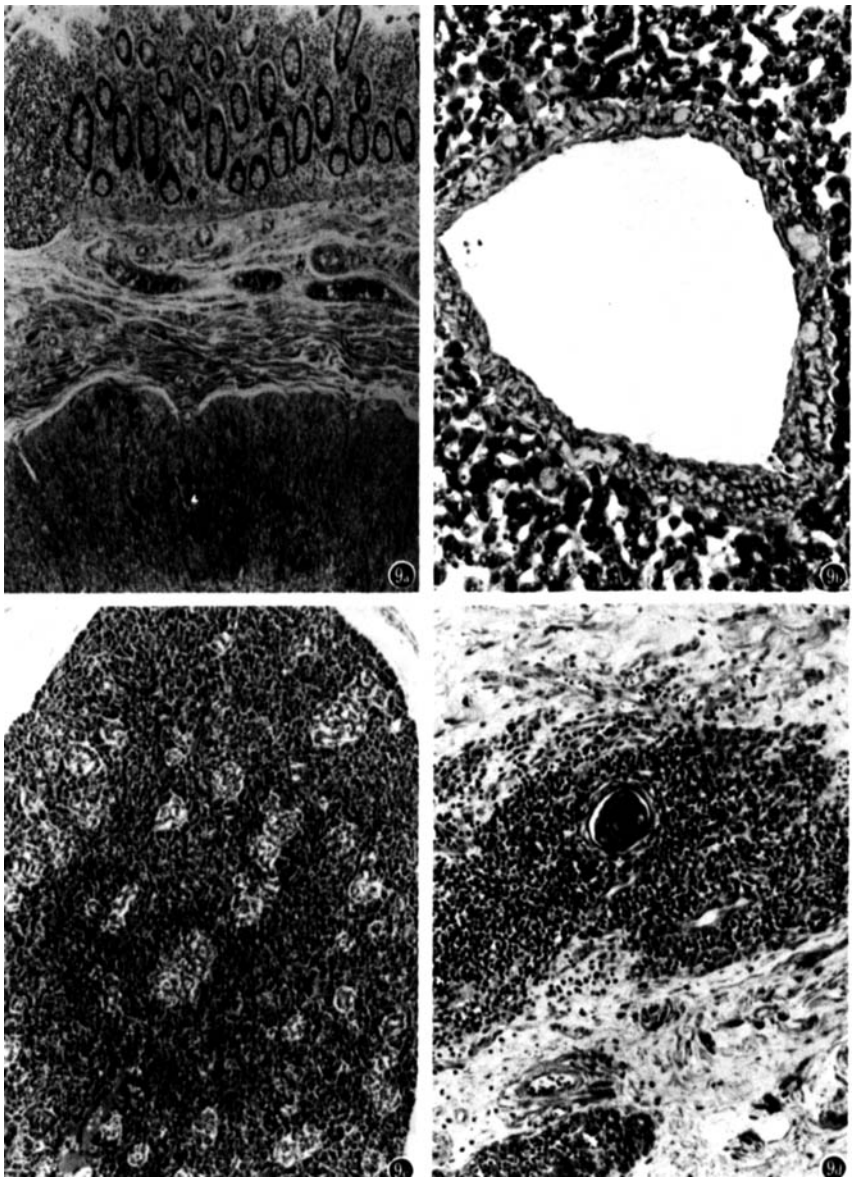


Fig. 9. a. Marked increasing of collagen fiber bundles in submucosa of the descending colon. El. M.T., × 20. 9b. Moderate thickening of the liver vein by collagenous tissue. El. M. T., × 50. 9c. Increase in number of small inslets in the pancreas tail. H.E., × 20. 9d. Thymus showing cortical atrophy and well preserved medulla with Hassall corpuscle. H. E., × 50.

while the medulla was well preserved with many Hassall corpuscles, some of which were calcified (Fig. 9d). Fat infiltration was formed occasionally on microscopical sections.

The lymph nodes were atrophic. Small lymphatic nodules were present in the

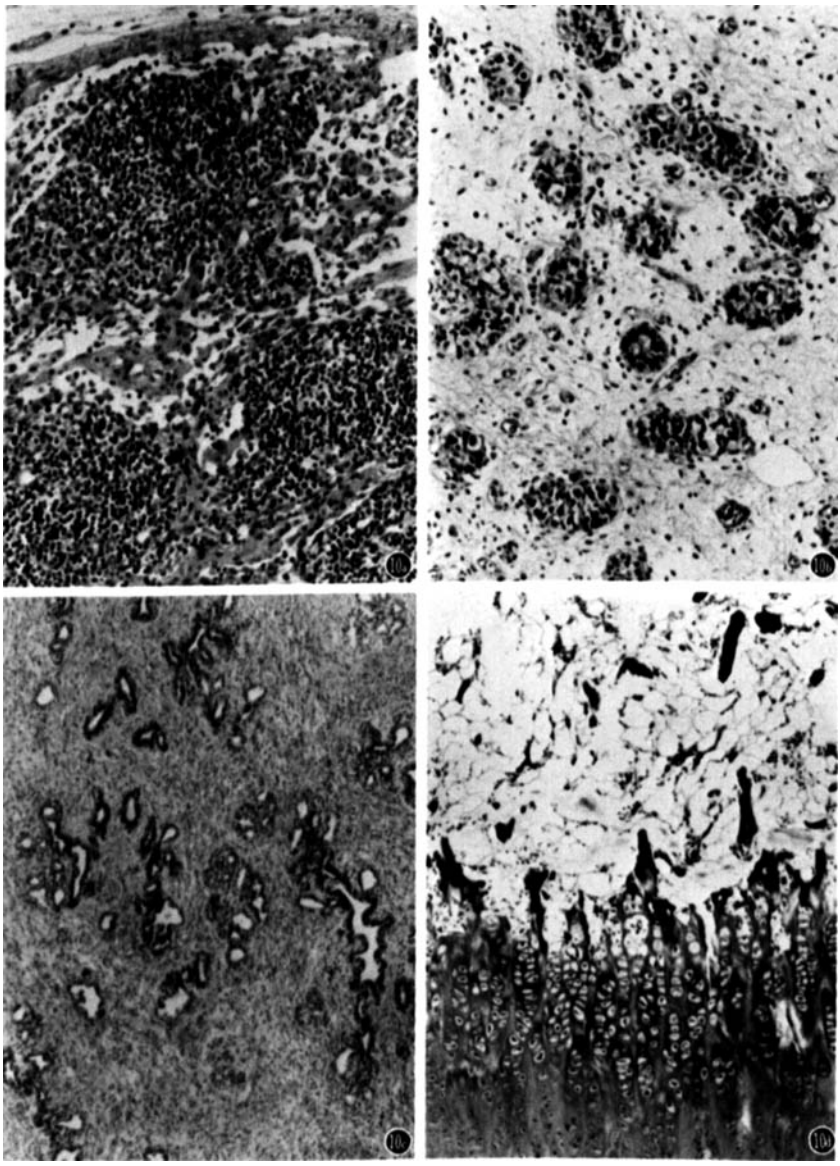


Fig. 10a. Small lymphatic nodule in the atrophic mesenteric lymph node. H.E., × 50. 10b. Underdeveloped seminferous tubuli embedded in edmatous stroma. H.E., × 50. 10c. Antepuberal state of the prostate. H.E., × 20. 10d. Slightly irregular column of hypertrophied cartilage cells at the distal epiphyseal growth zone of the left femur. Poor bone trabeculae. H.E., × 20.

atrophic cortical zone (Fig. 10a). The spleen weighed 50 g and was slightly swollen. Microscopical study showed many small lymphoid follicles, some of which had germinal center.

Pituitary gland weighed 0.3 g and acidophils were decreased slightly in number, although an exact differential cell count was not done. The left adrenal gland weighed 2.5 g, the right 2.9 g and both were encapsulated with thick collagenous tissue. The architecture was normal and the cell cords were atrophic on histological sections. The thyroid gland weighed 3.7 g and was not remarkable. The four parathyroid glands were identified and normal sized. They were mainly composed of water clear cells and no oxyphile cells were present. The left testis weighed 4.2 g and the right 3.1 g. A small number of underdevelopped seminiferous tubuli were embedded in edematous stroma and some of them contained calcium sands (Fig. 10b). The prostate was antepubertic and not remarkable (Fig. 10c).

Osseous chondral junction of the ribs was rosary-like thick. The calvarium and the cortex of the left femur were very thin. The distal epiphyseal plate of the femur was present. Microscopical study of the distal end of the femur showed that columns of hypertrophied cartilage cells were slightly shorter and irregular in shape than usual (Fig. 10d). The bone trabecules were very poor. The marrow of the femur was fatty, and in contrast that of vertebrae, sternum, and ribs was normal.

Discussion

The present case is the 13th autopsy report in the literature. **Table 1** shows the causes of death and main pathological findings of cardiovascular system, brain, and skin in all autopsy cases of progeria. It shows that the cardiovascular damage is one of the most important findings in autopsy cases.

Ten of 13 cases including our case died of congestive cardiac failure or coronary heart disease. In cases 4, 5 and our case, acute or healed myocardial infarct was diagnosed by ECG. Typical myocardial infarct was found in the anteroseptal region of cases 4 and 5. The former was proved only macroscopically. In case 3 multiple small foci showing all stages of myocardial infarct were found besides a recent septal infarct and case 9 had numerous infarcts in the anteroseptal region. The coronary arteries of these four cases revealed a severe degree of coronary arteriosclerosis and were almost or completely occluded. This severe coronary arteriosclerosis might have played an important role for myocardial infarct. The pathological findings observed in our case were similar to subendocardial infarct caused by severely narrowed coronary sclerosis observed in the aged. The subendocardial infarcts are usually not massive like transmural infarct but scattered or laminal in the inner half of the left ventricular wall and sometimes they are accompanied with small foci of myocardial necrosis in various stages. They are located in the most peripheral areas supplied by severe sclerotic coronary arteries. Hydropic degeneration of cardiac muscle fiber are also presented as small foci in the subendocardial and perivascular layer of the infarcted area. Thus the subendocardial myocardial damages may be circulatory in

Table 1. *Cause of Death and Main Pathologic Findings of*

No. cases	Authors	Age • Sex	Cause of death	Heart	
				Myocardium	Coronary-sclerosis
1	Gilford	18 M		121 gr	(#), Occlusion (+), Calcifi.(+)
2	Orrico *et al.*	21 M		125 gr.	
3	Talbot *et al.*	7.6 M	Coronary thrombosis	150 gr. Recent MI in septum. Small foci of MI in various stage	(#), Occlusion of LAD. Calcifi. (+)
4	Manschot	27 M	C.C.F.	220 gr. Old anteroseptal MI.	Calcified tube Occlusion(−)
5	Atkins	11.4 M	C.C.F.+ acute MI	110 gr, 1 month old anteroseptal MI. Mural thrombosis	(#), pinhole of coronary ostia, LAD. Calcifi.(+)
6	Rosenthal *et al.*	11 F	Traumatic epidural hematoma	95 gr. no change	slight
7	Gabr *et al.*	9 F	general convulsion	85 gr. Large patchy fibrosis.	Subintimal fibrosis
8	Makous	12.6 M	C.C.F.+ Gastro-intestinal infection	Large focal scar ischemic myocardial damages	(#),Occlusion of LAD
9	Macmanara	10 F	C.C.F.	175 gr numerous MI in anteroseptal region	Stenosis Calcifi.(+)
10	Reichel *et al.*	17 M	C.C.F.	Focal fibrosis Interstitial fibrosis	minimal
11	Reichel *et al.*	11.6 M	C.C.F.	Focal fibrosis Interstitial fibrosis	(+) patent
12	Ishii	20 F	Peritonitis	190 gr. No changes	(+) patent
13	Shozawa *et al.*	11.5 M	C.C.F. Sudden death	200 gr. Anteroseptal subendocardial fibrosis, Focal myocardial necrosis	(#), pinhole of LAD, RCA. Calcifi.(+)

C.C.F.; Congestive cardiac failure. Calcifi.; Calcification. LAD.; Left anterior descending artery. RCA.; Right coronary artery. MI; Myocardial infarct. Cerebral inf.; Cerebral infarct.

origin and laminal, scattered form of myocardial infarct fibrosis depends upon the degrees of development of collateral circulation in coronary artery system.[2]

Patchy and focal necrosis or fibrosis was found in cases 7, 8, 10, and 11 and was accompanied with interstitial fibrosis in the latter two cases. Anterior descending coronary artery of case 8 had severe coronary sclerosis and was occluded. The other

Cardiovascular System, Brain and Skin of 13 Autopsy Cases with Progeria

Calcifi. of cusp	Atheroscl. of aorta	Arterioscl. of other arteries	Brain	Skin
Ant. mitral leaflet, Aortic valve cusps	Aortic arch(+) Calcifi.(+)	Axillar arrtery		
	(+)	Basilar artery (+)	Atrophy of zona centrale	
Annulus fibrosus	(+)	Mesenterial, lienal and adrenal art.	Subdural hematoma	Atrophy in scalp. Subcutanous fibr. of abdomen
Aortic valve cusps	(+) calcifi.(+)	Arteries of nearly all organs	1475 gr. normal	thin atrophic
Ant. mitral leaflet	(+) Calcifi. (+)	Axillar art. Calcifi.(+)	1300 gr. Small infarct of left frontal lobe	Increase of hyaline in abdomen dermis leg; normal
	(+)	Mesenterial artery	1351 gr. not unusal	Scleroderma-like
	(±)	Great vessels Arteries of pancreas and thyroid		Scleroderma
Ant. mitral leaflet, Aortic valve cusps	(+) Calcifi.(+)			Atrophy
	(+) Ulcer			Hyperkeratosis
Post. mitral leaflet	(−)			
	Early changes			
		slight		Scleroderma-like Elastotic degeneration of dermis
	(+) Calcifi.(+)	Great vessels of extremities and organs	1170 gr. Right cerebral inf. Pinhole of int. carotid art.	Scleroderma-like

3 cases showed only slight intimal thickening. REICHEL *et al*,[21] described that focal fibrosis and necrosis of cases 10 and 11 should have been originated from general disorder of connective tissue, because the subendocardial coronary arteries were patent and the intramyocardial were free of pathologic process. OKADA[18] pointed out that microthrombi of intramyocardial arteries were frequently present in fresh focal

myocardial necrosis, but was decreased in frequency in focal fibrosis. SHOZAWA[26] stated that focal coagulation necrosis of myocardial fibers caused by ischemia were present in arterial site of microcirculatory bed and myocytolytic lesions induced by coronary insufficiency in venous site. Therefore, patchy and focal myocardial fibrosis in progeria might have been also caused by a local microcirculatory disturbance based on coronary insufficiency. No myocardial damage was described in cases 2, 6 and 12. Cases 6 and 12 died accidentally of head trauma and of peritonitis, respectively and had only minimal intimal thickening in the coronary arteries. In spite of severe coronary sclerosis no myocardial damage was reported in case 1.

The heart of over 200 g was found only in case 4. However, no discussion has been made about hypertrophy of cardiac muscle fibers in progeria. The height and body weight of the present case was smaller than that of a boy of the same age (138. 5 cm and 29 kg.) However, his heart was heavier than the average heart weight of the same age (150 g). The average diameter of the cardiac muscle fiber and length of the nucleus was larger than usual, but was within the upper limit of normal adult hearts.[9,12] Hypertrophy and dilation of the heart may have been induced by generalized arteriosclerosis and cardiac failure owing to myocardial damages.

Calcification of the mitral valve leaflet, aortic valve cusp or annulus fibrosus was described in cases 1, 3, 4, 5, 8, and 10. However, no calcification was found in the present case.

Though moderate or mild atheromatous changes were seen in the aorta of all autopsy cases, arteriosclerotic changes of the arteries were described in about a half of the cases and intimal calcification in coronary artery of cases 1, 3, 5, and 9 and in other arteries of cases 1 and 5. Mural calcification was seen in small arteries of the brain of case 10. Arteriosclerosis, focal atherosclerosis of the anterior mitral leaflet and calcification of annulus fibrosus are usually prominent in the aged.[16] Thus these findings in progeria may be one of the most important manifestation of premature aging and they may be caused by metabolic disorder in connective tissue.

Cortical atrophy of the anterior central gyrus was described in case 2 and a thumb-tip-sized old cerebral infarct of the left superior frontal gyrus and cingulate gyrus in case 5. In the former small arteriosclerotic plaques of the basilar artery was seen and no changes in the latter. In the present case, there was an old massive cerebral infarct in the left parietal lobe supplied by the middle cerebral artery and severe arteriosclerosis of the internal carotid arteries with pin-point lumen at the level of siphon. The cerebral infarct may have been induced by the same cause-and-effect relationship as happened in subendocardial myocard damages. An accumulation of lipofuscin pigments in nerve cells were described only in case 10. The pigments, which are known to accumulate as a function of age[20] are also present in the other pathologic condition. Neither lipofuscin nor senile plaque was observed in the present case.

The pathologic process of the brain in progeria may not be premature but secondary in origin. It is well known that both heart and brain are postmitotic organs

and the number of heart muscle cells as well as nerve cells increases to maximum within a short time after birth.[10] This may be one of the reasons that organic changes of vascular origin are frequently presented in the heart and brain of progeria.

Histological findings of the skin were described in only 2/3 of autopsy cases and not systematically. Atrophic skin was observed in case 4, in scalp of case 3, and with appendageal atrophy in case 8. Typical scleroderma was seen in case 7, scleroderma-like changes in cases 6 and 12, and increasing of collagen or hyaline in dermis in abdomen of cases 3 and in case 6. Elastotic degeneration in upper dermis was seen only in paraumblical area of case 12. Although the skin change was different in each area of cases 3, 5, and 12, an increase of collagen and hyaline in dermis and subcutaneous tissue were found to be main pathologic process of the skin in progeria. The skin of the present case was similar to case 6. Hypogenesis of the nails of the present case as well as atrophy and decrease in number of the appendages may suggest dysplastic changes of the skin.

The thymus was atrophic in cases 2, 4, 5, and 12. On the other hand, it weighed 48.3 g in case 1 and 32 g in case 7. Atrophy of the thymus and lymph nodes might indicate abnormalities of immunity in the present case. The decrease in T-cells in lymphocyte subpopulation and the increase of anti DNA antibody and antibody for microsome of thyroid gland was clinically detected in this case. In Warner syndrome and over 90 years aged persons,[8] immunological abnormalities have been clinically reported. Hypofunction of the immune system may be one of the most important manifestation of premature aging in progeria.

Pituitary gland weighed 0.3-0.4 g and showed normal size in most cases of progeria (cases 1, 2, 4, 5, 7, and 12). However, in case it weighed 1.91 g in spite of normal size and 0.6 g in case 3. A decreased number of eosinophilic cells was described in cases 4 and 5, but on the contrary an increase in case 7. The pituitary gland of the present case was normal in size and no significant morphological finding was found except for a slight decrease in eosinophilic cells. GILFORD and ORRICO *et al.* have suggested an abnormality in the pituitary gland. MANSCHOT mentioned that progeria should be regarded as a particular form of pituitary dwarfism with inadequate development derived from mesenchyms. Since ROSENBLOOM[23] pointed out a normal response of growth hormon in progeria in 1970, the cause of progeria should not be attributed to the pituitary gland.

Atrophic seminiferous tubuli of the testis was reported in case 2, prepuberal testis in case 5, and normal spermatogenesis in case 4. Accumulation of lipofuscin was demonstrated in cases 10 and 11. In the case of a 7 and 1/2 years old boy who received progestrone therapy (case 4), a fair number of early form of spermatogenetic series was seen in small seminiferous tubuli and the prostate showed a postpuberal state. Histology of the present case might indicate that the cause of atrophic testis was not premature but hypoplastic in origin.

Characteristic roentgenographic abnormalities are found in the skull, facial bones, thoracic cage, long bone, and pharanges, and there is a marked delay in bone healing

after fracture in progeria.[17,22,24] It is generally accepted that these disorders of the bone system are not only caused by primary bone disturbance but are modified by secondary changes based on vascular and muscular alteration.[22] However, abnormalities of the bone system were not systematically described in the autopsy cases. A thin skull was described in cases 1,3,4,5, and 7, thin cortex of femur in cases 4 and 7, osteomalacia of vertebrae in case 5, and fibrous clavicles in case 7. In case 6 and the present case, column of cartilage at the epiphyseal growth zone was short and irregular in size and shape.

Besides the above discussed findings, many other pathological findings of other organs were described in autopsy reports. However, they are not specific for progeria.

The etiology of progeria is still unclear at present. Myocardial damages and cerebral infarct, which may be the main cause of death are not specific pathological findings for progeria, but are secondary to severe intimal thickening of the artery system. It is generally accepted that morphological characteristics for progeria is an abnormal increasing of collagen in the connective tissue. A study of scleroprotein[30] of progeria has shown a physicochemical abnormality of skin collagen, incoporation of labelled glucose and proline, and uptake of oxygen into both cells and extracellular collagen. In recent years, shortened life span of cultured fibroblasts and deficient DNA repair have been reported in progeria.[3,7] In the present case, hyaluronuria was detected and a low growth rate and shortened life span of skin fibroblasts was observed on cell culture. These findings suggest that progeria is not resulted from premature aging but is caused by disturbance in connective tissue. Nowadays it is generally thought that progeria may be caused by mesenchymal dysplasia of autosomal recessive disorder.[29] Further investigations of abnormal metabolism of the connective tissue in progeria on a molecular level are necessary.

References

1. Atkins, L.: Progeria: Report of a case with post-mortem findings. New England J. Med. **250**: 1065-1069, 1954.
2. Balordi, G.: Different types of myocardial necrosis in coronary heart disease: a pathophysiologic review of their functionsl significance. Am. Heart J. **89**: 742-752, 1975.
3. Danes, S.: Progeria: A cell culture study on aging. J. clin. Invest. **50**: 2000-2003, 1971.
4. De Busk, F.L.: The Hutchinson-Gilford progeria syndrome. Report of 4 cases and review of the literature. J. pediat. **80**: 697-724, 1972.
5. Gabr, M., Hashem, N, Hashem, M., Fahm, A., and Safouh, M.: Progeria, a pathologic study. J. pediat. **57**: 70-77, 1960.
6. Gilford, H.: Progeria; A form of senilism. The Practitioner **73**: 188-217, 1904.
7. Goldstein, S.: Life span of cultured cells in progeria. Lancet **1**: 424, 1969.
8. Goto, M., Horiuchi, Y., Okumura, K., and Tada, T.: Immunological abnormalities of aging; An analysis of T lymphocyte subpopulation of Werner's syndrome. J. Clin. Invest. **64**: 695-699, 1979.
9. Hirosawa, K: Evaluation of endocmyocardial biopsy through study of cardiomyopathy: Sekiguchi, M., Olsen. E.G.J. (Editor): Cardiomyopathy, clinical, pathological and theoretical aspects, p. 197, Univ. Tokyo Press, Tokyo, Univ. Park Press, Baltimore, 1980.
10. Hort, W.: Quantitative histologische Untersuchungen and wachsenden Herzen. Virchow

Arch. Bd. 323 : 223-242, 1953.
11. ISHII, T. : Progeria : Autopsy report of one case, with a review of pathologic findings reported in the literature. J. Am. Geriat. Soc. 24 : 193-202, 1976.
12. LINZBACH, J.A. : Über bas Längenwachstum der Herzmuskelfasern und ihre Kern in Beziehung zur Herzdilatation. Virchow Arch. 328 : 165-181, 1956.
13. MACNAMARA, B.G.P., FARN, K.T., MITRA, A.K., LLOYD, J.K., and FOSBROOKE, A.S. : Progeria : Case report with long-term studies of serum lipids. Arch. Dis. Child. 45 : 553-559, 1970.
14. MAKOUS, N., FRIEDMAN, S., YAKOVAC, W., and MARIS, E.P. : Cardiovascular manifestations in progeria. Report of clinical and pathologic findings in a patient with severe arteriosclerotic heart disease and aortic stenosis. Am. Heart J. 64 : 334-346, 1950.
15. MANSCHOT, W.A. : A case of progeronanism (Progeria of Gilford) Acta Paediat. 39 : 158-164, 1950.
16. Mc MILLAN, J.B. and LEV, M. : The aging heart. 11 The valves. J. Gerontol. 19 : 1-14, 1964.
17. MOEN, C. : Orthopaedic aspects of progeria. J. Bone Joint Surg. 64-A : 542-546, 1982.
18. OKADA, E. : Pathological study on intramyocardial focal focal lesions with special reference to intramyocardial microthrombi. J. Jap. Coll. Angiology. 21 : 29-41, 1981.
19. ORRICO, J. and STRADA, F. : Etude anatomo-clinique sur un cas de manisme sénile (progérie). Arc. Med. Enfants. 30 : 385-398, 1927.
20. REICHEL, W. : Lipofuscin pigment accumulation as a function of age and distribution in rodent brain. J. Gerontol. 23 : 71-78, 1968.
21. REICHEL, W. and GARCIA-BUNUEL, R. : Pathologic findings in progeria : Myocardial fibrosis and lipofuscin pigment. Am. J. Clin. Pathol. 53 : 243-253, 1970.
22. REICHEL, W., BAILELY II,J.A., ZIGEL, S., GARCIA-BUNUELS, R. and KNOX, G. : Radiological findings in progeria. J.Am. Geriat. Soc. 19 : 657-674, 1971.
23. ROSENBLOOM, A.L., KARACAN, I.J., and DE BUSK, F.L. : Sleep characteristics and endocrine response in progeria. J. Pediat. 77 : 692-695, 1970.
24. ROSENTHAL, I.M., BRONSTEIN, I.P., DALLENBACH, F.D., PRUZANSKY, S., and Rosenwald, A. K. : Report of a case with cephalometric roentgenograms and abnormally high concentrations of lipoproteins in the serum. Pediatrics. 18 : 565-577, 1956.
25. SHIMADA, K., HASHIMOTO, T., YATABE, M., TUJI, E., and HIGASHI, O. : A case of Hutchinson-Gilford syndrome. Nihon Shonika Gakkai Shi : 86 : 786-793, 1982 (*in Japanese*).
26. SHOZAWA, T., KAWAMURA, K., and OKADA, E. : Study of intramyocardial microangioarchitecture with respect to pathogenesis of focal myocardial necrosis. Bibl. Anat. 20 : 511-516, 1981.
27. TALBOT, N.B., BUTLER, A.M.m PRATT, E.L., MAC LACHLAM, E.A., and TANNHEDMEM, J. : Progeria : clinical, metabolic and pathologic studies on a patient. Am. J. Dis. Child. 69 : 267-280, 1945.
28. TOKUNAGA, M., WAKAMATSU, E., SATAKE, S., AOYAMA, K., SAITO, K., SUGAWARA, M., and YOSIWAWA, Z. : Hyaluronuria in a case of progeria (Hutchinson-Gilford syndrome) J. Am. Geriat. Soc. 26 : 296-302, 1978.
29. VIÉGAS, J., SOUZA, P.L.R., and SULZANO, F.M. : Progeria in twins. J. Med. Genet. 11 : 304-386, 1974.
30. VILLEE, D.B., NICHOLS, G., and TALBOT, N.B. : Metabolic studies in two boys with classical progeria. Pediatrics. 43 : 207-216, 1969.