Pathology of Malignant Nephrosclerosis with Special Reference to the Difference between Histologic Manifestations of Pure and Exacerbated Forms

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FUJIMOTO, T. Pathology of Malignant Nephrosclerosis with Special Reference to the Difference between Histologic Manifestations of Pure and Exacerbated Forms. Tohoku J. exp. Med., 1978, 125 (2), 135-153 — Fourteen autopsied cases of malignant nephrosclerosis were classified into 6 of pure form in which syndrome of malignant hypertension developed from the beginning of the disease, and 8 of exacerbated form with appearance of the syndrome in the course of essential hypertension. Pathohistological study of these cases elucidated the differences in histologic manifestations between pure and exacerbated forms of malignant nephrosclerosis as to which little had been known as yet. In the pure form arterioles and small arteries characteristically demonstrated acute or recent lesions such as fibrinoid necrosis and hemorrhage into intima, and intimal cellular hyperplasia of somewhat longer duration, whereas in the exacerbated form coexistence of vascular lesions of various intensities and durations, acute (fibrinoid necrosis and hemorrhage), intermediate (intimal cellular hyperplasia) to chronic (sclerosis and lamellar elastosis), and superposition of more recent vascular lesions on more advanced or older ones were noted. Superposition of vascular alterations was interpreted to be not necessarily specific for exacerbated form but histologic manifestation of recurrence which is liable to be the case more frequently in exacerbated form than in pure form in the longer course of essential hypertension or of malignant hypertension. Some other related problems were also considered and discussed. — hypertension; malignant hypertension; malignant nephrosclerosis; nephrosclerosis

Fahr (1925) classified sclerotic diseases of the kidney into benign nephrosclerosis characterized by pure arteriosclerotic changes and malignant nephrosclerosis in which productive endarteritis, periarteritis, and angioneerosis were most predominant among the pathologic features in his handbook description of Bright’s diseases. Throughout his documents he did not acknowledge a relation between

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hypertension and nephrosclerosis. On the contrary, Volhard (1931) advocated that essential hypertension (“roter Hochdruck”) is followed, through the stage of benign nephroangiosclerosis which is associated with hypertension and no renal insufficiency, by malignant nephroangiosclerosis accompanied by “blasser Hochdruck” (“Kombinationsform”). It may surely be said that detailed characterization of pathologic anatomy of malignant nephrosclerosis was accomplished by Schürmann and MacMahon (1933) through their extensive and systematic studies. One of the most characteristic features of their works lay in the systematic description of both structural changes of layers of vascular walls along the course of arterial trees in the whole body and alterations of various organ tissues. The histological changes consisted of hyperplasia, histolysis with or without following organization, and necrosis, which usually developed in order of vascular calibers from the proximal segments of arteries (larger and small arteries) to the distal segments (arterioles and capillaries). They also clarified that there are two forms of malignant nephrosclerosis, genuine form coming from essential hypertension, and exogenous-toxic form characterized by acute onset of disease with renal impairment. However, even the works of Schürmann and MacMahon (1933) did not refer to the difference between histologic manifestations of two forms of malignant nephrosclerosis. Recently, Bohle et al. (1973) classified malignant nephrosclerosis into two groups, i.e., primary and secondary malignant nephrosclerosis. Still they did not inform us of precise difference between histologic characteristics especially of vascular lesions in two groups of malignant nephrosclerosis.

In 1967 Fujimoto et al. reported an autopsy case of renovascular hypertension due to unilateral fibromuscular hyperplasia of renal artery in a 24-year-old female of 3 years' duration, in which the patient had developed acute exacerbation with syndrome of malignant hypertension following aortography, terminating in uremic death in 8 days. In this case it was remarkable that the left kidney which had been almost free from stenosis of homolateral renal artery demonstrated advanced atrophy and sclerosis of renal tissues and recent fibrinoid necrosis of intima superimposed on sclerosis of interlobular arteries, whereas the right kidney with arterial stenosis had fibrinoid necrosis of neither thickened nor sclerotic intima of arterioles and resulting acute atrophy and necrosis of renal tissues.

It is the purpose of this paper to present pathohistological findings of autopsy cases of malignant nephrosclerosis and discuss some problems including those mentioned above.

**Materials and Methods**

The materials consisted of 14 autopsied cases of malignant nephrosclerosis collected from the Departments of Pathology, Osaka City University Medical School, Chiba University School of Medicine, and Sapporo Medical College (Table 1). These cases were divided into 6 cases of pure form, 5 males and 1 female, 24 to 42 years of age, with 3 to 17 months' duration of syndrome of malignant hypertension (Group 1), and 8 cases of exacerbated form, all males, 40 to 62 years of age, with 17 months' to 9 years' duration of
symptoms of hypertension and period of exacerbation with syndrome of malignant hypertension between last 1 month and 3 years (Group 2). Cases 12 and 14 of Group 2 had renal biopsies 9 months and 47 days prior to death, respectively. These 14 cases conformed to diagnostic criteria of malignant hypertension of the Subcommittee of the Japanese Association for Cerebro-Cardiovascular Disease Control (Shigiya et al. 1974): 1) diastolic blood pressure almost invariably over 130 mmHg before anti-hypertensive treatment, 2) grade IV of retinopathy according to Wagener and Keith (1939), 3) progressive deterioration of renal function leading to renal insufficiency, and 4) a progressive downward course not infrequently associated with cerebral symptoms and/or cardiac insufficiency. Case 6 of Group 1 and Cases 9, 10, 12, and 14 of Group 2 were subjected to administrations of anti-hypertensive drugs including direct vasodilators and sympathetic blocking drugs during their hospitalization, and lowering of elevated blood pressure and some improvement of symptoms were recorded in Cases 6 and 9, while no effect was obtained in Cases 10, 12, and 14.

Tissue blocks of these cases were taken from kidneys, heart, lungs, spleen, liver, pancreas, adrenals, digestive tract, brain, and aorta, formalin-fixed, embedded in paraffin,

<table>
<thead>
<tr>
<th>Group No.</th>
<th>Case No.</th>
<th>Autopsy No.</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Duration of symptoms (period of exacerbation)</th>
<th>Remarks</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Chiba Univ.</td>
<td>148–1956</td>
<td>24</td>
<td>M</td>
<td>3 mos.</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Osaka City Univ.</td>
<td>2631</td>
<td>27</td>
<td>M</td>
<td>3 mos.</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Osaka City Univ.</td>
<td>2677</td>
<td>42</td>
<td>M</td>
<td>3 mos.</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Chiba Univ.</td>
<td>46–1963</td>
<td>40</td>
<td>F</td>
<td>4 mos.</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Chiba Univ.</td>
<td>140–1963</td>
<td>40</td>
<td>M</td>
<td>14 mos.</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Chiba Univ.</td>
<td>68–1959</td>
<td>26</td>
<td>M</td>
<td>17 mos.</td>
<td>Anti-hypertensive therapy with some improvements</td>
</tr>
<tr>
<td>7</td>
<td>Sapporo Med. Col.</td>
<td>2539</td>
<td>62</td>
<td>M</td>
<td>17 mos. (1 mos.)</td>
<td>Marked hypoplasia of right kidney</td>
</tr>
<tr>
<td>8</td>
<td>Sapporo Med. Col.</td>
<td>2261</td>
<td>40</td>
<td>M</td>
<td>3 yrs. (2 mos.)</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Sapporo Med. Col.</td>
<td>2844</td>
<td>61</td>
<td>M</td>
<td>3 yrs. (2 mos.)</td>
<td>Anti-hypertensive therapy with some improvements</td>
</tr>
<tr>
<td>10</td>
<td>Osaka City Univ.</td>
<td>3015</td>
<td>49</td>
<td>M</td>
<td>2 yrs. (3 mos.)</td>
<td>Anti-hypertensive therapy without responses</td>
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<td>11</td>
<td>Chiba Univ.</td>
<td>54–1957</td>
<td>50</td>
<td>M</td>
<td>4 yrs. (3 mos.)</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Chiba Univ.</td>
<td>87–1958</td>
<td>48</td>
<td>M</td>
<td>6 yrs. (14 mos.)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 1. Outline of the Cases**
cut at 2 to 3 microns, and serial sections were used when necessary. The histological sections were treated with hematoxylin-eosin stain (HE stain), periodic acid-Schiff's stain (PAS stain), periodic acid-methenamine silver stain (PAM stain), Mallory-Heidenhain's stain, Weigert's resorcin-fuchsin and van Gieson's stain, Weigert's fibrin stain, phosphotungstic acid-hematoxylin stain (PTAH stain), and Bielschowsky's silver impregnation. Fatty changes were studied in frozen sections stained with sudan III.

Results

Kidneys (examined in 14 cases)

Kidneys were somewhat to considerably enlarged, with rather smooth surfaces not infrequently associated with punctate hemorrhages in the majority of cases, while they were shrunken and indurated to some degree with finely granular surfaces in the other cases. Combined weight of bilateral kidneys ranged between 230 and 500 gms. in the majority of cases, but it was reduced below 200 gms. in 4 cases. It was remarkable that the weight of kidneys was only 68 gms. (left 35 gms. and right 33 gms.) in Case 6 of Group 1 with 17 months' duration. On the cut surface, medulla was dark red in contrast to pale anemic cortex, and thickness of cortex became considerably reduced in the case of shrunken kidneys.

Glomeruli. Variable numbers of glomeruli showed collapse (Fig. 1), subsequent sclerosis, or hyalinization in all cases. Accumulation of neutrophiles was sometimes seen. Swelling of endothelial cells and swelling and thickening of loop walls with cellular increases (Fig. 2) were encountered especially in cases of Group 2. Not infrequently associated with these glomerular changes were swelling, proliferation, and hyaline droplet degeneration of epithelial cells. In 2 cases of Group 2, foam cell reaction of endothelial cells was found. Fibrinoid necrosis of loop walls often associated with aneurysmal dilatation was visible in 4 cases. The site of this lesion was tinctorial like fibrin, i.e., stained red with HE stain, brightly red with Mallory-Heidenhain's stain, purple with Weigert's fibrin stain, and blue with PTAH stain, but appeared finely granular or homogeneous in contrast to fibrin appearing as threads. In this area, cellular elements showed destruction or dissolution, and the fibrillar framework of the tissue was dispersed and fragmented. Sudan III stain revealed fatty deposits in this area. Thrombosis of glomerular capillaries was not infrequently seen together with this lesion. Compensatory hypertrophy of glomeruli was somewhat distinct in Group 2.

Bowman's capsules. Proteinaceous leakage, and sometimes fibrinous exudation into capsular spaces were visible in a few cases. Focal epithelial crescents (Fig. 3) were chiefly recognized in cases of Group 1, whereas fibrous-hyaline thickening of capsular walls in cases of Group 2.

Urinary tubular tissues. Moderate to severe atrophy of proximal convoluted tubular epithelial cells was significantly visible, which appeared more predominant than collapse and following hyalinization of glomeruli, leading to crowding of glomeruli (Fig. 1). Associated with the epithelial atrophy were edematous thickening of interstitial tissue (Fig. 1) in the cases of short duration of symptoms and moderate to advanced sclerosis of the tissue (Fig. 3) in the cases of longer duration.
Hyaline droplet degeneration of proximal convoluted tubular epithelial cells was recognizable in association with increased leakage of protein into capsular spaces. Compensatory hypertrophy of proximal convoluted tubular tissue was more or less visible in cases of longer duration, which was somewhat remarkable in 3 cases of Group 2. In contrast to distinct atrophy and sclerosis of proximal convoluted tubular tissue atrophy of distal convoluted tubular epithelial cells associated with edematous thickening of interstitial tissue was mild throughout the cases examined. Nests of epithelial cells with clear cytoplasm and not clearly identified tubular lumens, which were surrounded by basement membrane and interstitial tissue almost composed of capillary networks, probably derived from distal convoluted tubular tissue (Fig. 4), were recognized especially in cases of Group 2.

Anemic infarction of kidney was encountered only in 1 case of Group 1. It was notable that moderate hyperplasia of juxtaglomerular cells (Fig. 5) appeared in 2 cases of Group 2. In the majority of cases was complication of pyelonephritis, mild to moderate, and focal in nature.

Arterioles and small arteries. In the afferent arterioles 3 cases of Group 1 and 2 cases of Group 2 demonstrated moderate to marked hyalinization of intima. Hemorrhage into intima was noticed in 1 case of Group 1 and 4 cases of Group 2. Fibrinoid necrosis of intima not infrequently extending to media (Fig. 6) was characteristically found in 5 cases of Group 1 and 4 cases of Group 2. The lesion was sometimes associated with thrombosis. In Case 6 of Group 1 and Case 9 of Group 2 fibrinoid necrosis was not recognizable. In the distal segments of interlobular arteries edema or histolysis of intima was markedly visible in 2 cases of Group 1 and slightly in 1 case of Group 2, while edematous-fibrous thickening or sclerosis of intima was only seen in 3 cases of Group 2. Intimal thickening with proliferation of reticular or spindle-shaped cells connected with their cytoplasmic processes and not infrequently associated with basophilic mucoid swelling of intercellular tissue (intimal cellular hyperplasia), moderate to severe, was recognizable in 1 case of Group 1 and 7 cases of Group 2. This kind of lesion was usually accompanied by atrophy and reduction in numbers of myofibers and interstitial sclerosis of media. In 5 cases of Group 2, concentric fibrous thickening of intima produced by elongation of proliferated cells and lamellar increase of collagenous fibers (concentric fibrosis) was seen. It was revealed by sudan III stain that intima with cellular hyperplasia or with concentric fibrosis was fat-laden just like the sites of fibrinoid necrosis. The conversion of intimal cellular hyperplasia to concentric fibrosis was ascertained in Case 14 of Group 2 on the basis of sequential study by renal biopsy and following autopsy. Hemorrhage into intima with cellular hyperplasia (Fig. 7) was recognizable only in 2 cases of Group 2. One of these cases showed also hemorrhage into intima with concentric fibrosis. Fibrinoid necrosis of not thickened intima was recognized in 1 case of Group 1 of longest duration and 3 cases of Group 2, while fibrinoid necrosis of sclerotic, already thickened intima, sometimes of its subendothelial layer (Figs. 8 and 9) or external layer adjacent to media (Fig. 10) in 5 cases of Group 2 was displayed. Sequential observations in Case 14 revealed that
Fig. 1. Collapse of glomeruli, and atrophy and edematous thickening of proximal convoluted tubular tissues. Edema or histolysis of intima of interlobular artery is seen. Case 1. Mallory-Heidenhain’s stain. \( \times 60 \).

Fig. 2. Swelling and thickening of glomerular loop walls with cellular increases. Case 10. PAS stain. \( \times 300 \).

Fig. 3. Collapse of glomeruli, atrophy and sclerosis of proximal convoluted tubular tissues, and focal epithelial crescent formation. Vacuolization of myofibers of media of interlobular artery is visible. Case 6. Mallory-Heidenhain’s stain. \( \times 60 \).

Fig. 4. “Endocrine kidney” structure, and fibrinoid necrosis of intima with cellular hyperplasia of distal segments of interlobular artery. Case 12. HE stain. \( \times 150 \).
Fig. 5. Hyperplasia of juxtaglomerular cells. Case 10. PAS stain. × 300.
Fig. 6. Fibrinoid necrosis of afferent arteriole. Case 4. HE stain. × 300.
Fig. 7. Hemorrhage into intima with cellular hyperplasia of distal segment of interlobular artery. Case 7. Left kidney. HE stain. × 300.
Fig. 8. Fibrinoid necrosis of subendothelial layer of sclerotic intima of distal segments of interlobular artery. Case 13. HE stain. × 150.
Fig. 9. Fibrinoid necrosis of subendothelial layer of sclerotic intima of distal segment of interlobular artery. Case 10. Weigert's resorcin-fuchsin and van Gieson's stain. × 150.

Fig. 10. Fibrinoid necrosis of external layer of sclerotic intima of distal segment of interlobular artery. Case 10. HE stain. × 150.

Fig. 11. Edema or histolysis and hemorrhage of intima of proximal segment of interlobular artery. Case 1. Mallory-Heidenhain's stain. × 150.

Fig. 12. Lamellar elastosis of proximal segment of interlobular artery. Case 12. Weigert's resorcin-fuchsin and van Gieson's stain. × 150.
Fig. 13. Intimal cellular hyperplasia of proximal segments of interlobular artery. Case 8. Weigert’s resorcin-fuchsin and van Gieson’s stain. × 150.

Fig. 14. Concentric fibrosis of intima of proximal segment of interlobular artery. Case 10. PAS stain. × 60.

Fig. 15. Intimal cellular hyperplasia in the luminal side of sclerotic intima of proximal segments of interlobular artery. Case 10. Weigert’s resorcin-fuchsin and van Gieson’s stain. × 150.

Fig. 16. Intimal cellular hyperplasia in the inside of intima with lamellar elastosis of proximal segment of interlobular artery. Case 10. Weigert’s resorcin-fuchsin and van Gieson’s stain. × 150.
fibrinoid necrosis occurred in the subendothelial layer of already sclerotic intima in 47 days after renal biopsy. Fibrinoid necrosis in the subendothelial layer or in the external layer of intima with cellular hyperplasia (Fig. 4) was intense in Group 2 (2 cases) and mild in Group 1 (2 cases). In 1 of the 2 cases of Group 2 (Case 13) fibrinoid necrosis of intima with concentric fibrosis was encountered as well. Sometimes associated with fibrinoid necrosis of the distal segments of interlobular arteries was thrombosis in the lumens. Fibrinoid necrosis irrespective of thickness of intima was not visible in Case 9 of Group 2. Two cases of Group 2 showed perinuclear vacuolization of myofibers of media. Fibrous thickening of adventitia was found in 1 case of Group 2. In the proximal segments of interlobular arteries edema or histolysis of intima (Figs. 1 and 11) was noted only in 2 cases of Group 1, while moderate to marked edematous-fibrous thickening or sclerosis of intima was present in 3 cases of Group 1 and 7 cases of Group 2. Mild to marked lamellar elastosis of intima (Fig. 12) was seen in 2 cases of Group 1 and 7 cases of Group 2. Four cases of Group 1 and 7 cases of Group 2 exhibited moderate to marked intimal cellular hyperplasia (Fig. 13). Three cases of Group 2 showed concentric fibrosis of intima (Fig. 14). In 4 cases of Group 2 moderate or slight intimal cellular hyperplasia which occurred in the luminal side of intima separated by thin elastic membrane from sclerotic intima of medial side or in the inside of intima showing lamellar elastosis was recognized (Figs. 15 and 16). Three cases of Group 1 demonstrated hemorrhage into intima (Fig. 11), whereas in Group 2 hemorrhage into intima with cellular hyperplasia was shown in addition to that into not thickened intima in 3 cases. One case of Group 2 exhibited hemorrhage into intima with concentric fibrosis. Moderate hypertrophy and hyperplasia of myofibers of media were noted in 3 cases of Group 1 and 1 case of Group 2. Five cases of Group 1 and 8 cases of Group 2 showed moderate perinuclear vacuolization of myofibers of media (Fig. 3). Decrease in numbers of myofibers and interstitial sclerosis of media were shown in 3 cases of Group 1 and all 8 cases of Group 2. Mild fibrous thickening of adventitia was encountered only in 2 cases of Group 1 of shortest duration. In the arcuate arteries 2 cases of Group 1 had edema or histolysis of intima. Mild to marked elastosis of intima appeared in 3 cases of Group 1 and 5 cases of Group 2. Sclerosis of intima was mild in 1 case of Group 1 of longest duration, while it was moderate to marked in 3 cases of Group 2. Marked intimal cellular hyperplasia was shown only in 2 cases of Group 1 of shortest duration. Two cases of Group 1 showed hemorrhage into intima. Mild hypertrophy and hyperplasia of myofibers of media were detected in 3 cases of Group 1 and 1 case of Group 2, whereas mild perinuclear vacuolization of myofibers was demonstrated in 4 cases of Group 1 and 7 cases of Group 2. Mild decrease in numbers of myofibers and interstitial sclerosis of media were recognized in 5 cases of Group 2 in contrast to occurrence of these changes only in 1 case of Group 1. Fibrous thickening of adventitia was seen in 1 case of Group 1 and 1 case of Group 2. The interlobar arteries showed edema or histolysis of intima in 1 case of Group 1 of shortest duration. Elastosis of intima was visible in 2 cases of Group 1 and 4 cases of group 2,
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and sclerosis of intima, moderate to marked, was shown in 2 cases of Group 2. Atherosclerosis of intima was encountered in 1 case of Group 2. Hypertrophy and hyperplasia of myofibers of media, slight, in 1 case, and slight vacuolization of myofibers and interstitial sclerosis of media in 2 cases were recognized.

Heart (examined in 11 cases)

The heart showed slight to moderate hypertrophy of left ventricle. In 3 cases the hypertrophy was concentric in nature, whereas in 8 cases it was associated with dilatation of the ventricle. Weight of heart ranged between 330 and 660 gms. Small myocardial scars or foci of fibrosis were recognized in most of the cases, and 1 case of Group 2 had basophilic mucoid degeneration of cardiac myofibers in some places. Arterioles showed edema or histolysis of intima and media in 5 cases of Group 1 and 3 cases of Group 2. Elastosis of intima was shown in 1 case of Group 2. Vacuolization of myofibers, and decrease in numbers of myofibers and interstitial sclerosis of media were seen in 3 cases of Group 2, and sclerosis and hyalinization of adventitia were seen in 1 case of Group 2. In the branches of coronary arteries lamellar elastosis of intima was recognizable in 1 case of Group 1, while sclerosis of intima in 4 cases of Group 1 and 2 cases of Group 2. Organization of thrombus and following recanalization, hypertrophy and hyperplasia of myofibers, vacuolization of myofibers, and decrease in numbers of myofibers and interstitial sclerosis of media, and sclerosis and hyalinization of adventitia were found in 2 cases.

Lungs (examined in 11 cases)

Cases examined except for 1 case showed mild to moderate congestion and edema of lungs, and 4 cases had sclerosis of alveolar walls. Hemorrhage and fibrinous extravasation into alveolar spaces were seen in 3 cases of Group 1 and 4 cases of Group 2, and 1 case of Group 2 demonstrated hyaline membrane formation. Mild intimal thickening of arterioles and small arteries were occasionally visible in 2 cases of Group 2.

Spleen (examined in 12 cases)

All cases had mild to moderate congestion, and 2 cases of Group 1 and 4 of Group 2 revealed sclerosis of pulp. In most of cases mild to moderate atrophy of lymph follicles was seen. Two cases had anemic infarctions. In the follicular arteries edema or histolysis of intima was more intense in Group 1 (4 cases) than in Group 2 (3 cases), whereas mild sclerosis of intima was recognizable in 4 cases of Group 2. Mild to moderate hyalinization of intima was visible in examined cases except for 1 case of Group 2, and in 3 cases of Group 1 marked hyalinization was also shown in some places. Intimal cellular hyperplasia, mild, was seen in 1 case of Group 2, and concentric fibrosis of intima was present in 1 case of Group 1 and 2 cases of Group 2. One case of Group 1 and 2 cases of Group 2 had hemorrhage into intima. Moderate fibrinoid necrosis of intima not infrequently extending to media was demonstrated in 3 cases of Group 1 and mild one in 2 cases of Group 2, while that of sclerotic intima was only seen in 3 cases of Group 2. Decrease in numbers of myofibers and interstitial sclerosis of media were somewhat clearly shown in Group 2. Edema and fibrous thickening of adventitia were recognized in some cases. In the trabecular arteries elastosis, sclerosis, and atherosclerosis of intima, and decrease in numbers of myofibers and interstitial sclerosis of media were shown in a few cases of Group 2.

Liver (examined in 12 cases)

All except for 1 case showed congestion, which was followed by centrolobular sclerosis of perivenular and -sinusoidal tissues in 2 cases. Fatty degeneration of hepatic cells was seen in 4 cases of Group 2. In the interlobular arteries edema or histolysis of intima was visible in 3 cases of Group 1 and 4 cases of Group 2, while sclerosis of intima was present in 1 case of Group 1 and 5 cases of Group 2. Elastosis of intima was demonstrated only
in 3 cases of group 2. Hyalinization of intima, though it was mild, was more frequently found in Group 1 (5 cases) than in Group 2 (2 cases). Fibrinoid necrosis of sclerotic intima was recognized only in 1 case of Group 2. Edema or histolysis of media, vacuolization of myofibers, mild hypertrophy and hyperplasia of myofibers, and slight to moderate decrease in numbers of myofibers and interstitial sclerosis of media were shown in 3 cases.

Pancreas (examined in 10 cases)

Each 3 cases of the two groups showed mild to moderate atrophy of the pancreatic tissue, and in 2 cases of group 1 and 1 case of Group 2 an increase of adipose tissue was seen. Edema and loosening of pancreatic tissue and intralobular fibrosis were shown in a few cases. One case had cystic dilatation of acinar tissue with retention of secretions. Focal necrosis of pancreatic tissue not infrequently associated with hemorrhage was seen in 1 case of Group 1 and 2 cases of Group 2. In the arterioles edema or histolysis of intima was seen in each 3 cases of the two groups, which appeared somewhat distinct in 1 case of Group 1. Sclerosis of intima was only seen in 1 case of Group 2. Hyalinization of intima was demonstrated in 3 cases of Group 1 and 2 cases of Group 2, which appeared more intense in the former. Moderate fibrinoid necrosis of intima was recognized in 2 cases of Group 1 and mild one in 1 case of Group 2, whereas fibrinoid necrosis of sclerotic intima, moderate, was visible only in 1 case of Group 2. Two cases of Group 1 had edema or histolysis of media, while 2 cases of Group 2 showed perinuclear vacuolization of myofibers of media. In the small arteries mild elastosis of intima was only recognizable in 1 case of Group 2. Mild to moderate sclerosis of intima was found in 1 case of Group 1 and 2 cases of Group 2. Hypertrophy, vacuolization, and decrease in numbers of myofibers, and interstitial sclerosis of media were recognized in 2 cases.

Adrenals (examined in 10 cases)

Cases except for two showed slight to moderate atrophy of cortex and lipiod depletion, and 1 case of Group 2 had focal interstitial sclerosis of cortical tissue. In the capsular arterioles edema or histolysis of intima was shown in each 4 cases of the two groups, and 1 case of Group 1 and 1 of Group 2 had intimal sclerosis. Concentric fibrosis of intima, mild, was seen only in 1 case of Group 2. Hyalinization of intima found in 4 cases of Group 1 appeared more intense than that in 2 cases of Group 2. Fibrinoid necrosis of intima, which extended to media in some places, was seen in 1 case of Group 1 and 1 case of Group 2, whereas fibrinoid necrosis of sclerotic intima was visible only in 1 case of Group 2. Edema or histolysis of media was found in 2 cases of Group 1 and 3 cases of Group 2. Vacuolization of myofibers of media was seen in 1 case of Group 2, and decrease in numbers of myofibers and interstitial sclerosis of media were recognized in 2 cases of Group 2.

Digestive tract (examined in 5 cases)

Cases 2 and 3 (Group 1) and Cases 10, 13, and 14 (Group 2) were examined. In Case 2 arterioles of ileum showed mild edema or histolysis of intima and media, and mild to moderate fibrinoid necrosis of intima associated with hemorrhagic ulcerative ileitis, and arterioles of appendix vermiformis had edema or histolysis of media. Case 3 had sclerosis of intima of arterioles in esophageal wall, intimal sclerosis and vacuolization of myofibers of media of arterioles of stomach and jejunum, and edema or histolysis of media of arterioles of colon. Case 10 demonstrated intimal sclerosis of arterioles of stomach, small intestine, and colon. Vacuolization of myofibers and edema or histolysis of media were seen in arterioles of colon in Case 13. Case 14 demonstrated edema or histolysis of intima and decrease in numbers of myofibers and interstitial sclerosis of media of arterioles in the gastric wall.

Brain (examined in 4 cases)

Brain was examined in Case 1 of Group 1 and Cases 7, 8, and 14 of Group 2. In Case 1 brain was markedly edematous and had multiple foci of softening. Arterioles showed moderate edema or histolysis of intima and media in many places. Case 7 had old foci of hemorrhage
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with hemosiderosis in the basal ganglia and right temporal lobe, edema or histolysis of intima and media of arterioles, and dilatation of periarteriolar spaces. In Case 8 edema or histolysis of intima and media of arterioles was moderately seen. In the brain of Case 14 hemorrhagic foci in the right internal capsule, lenticular nucleus, and right parietal lobe, old pigmented hemorrhagic foci in the dentate nucleus, small cysts due to softening in the lenticular nucleus, hemorrhage into right lateral ventricle, and moderate atherosclerosis of basilar arteries were exhibited. In this brain arterioles showed edema or histolysis of intima and media, dilatation of periarteriolar spaces, sclerosis, hemorrhage, and fibrinoid necrosis of intima, perinuclear vacuolization of myofibers, and decrease in numbers of myofibers and interstitial sclerosis of media.

Aorta (examined in 7 cases)

In Cases 2 and 3 of Group 1 and Cases 7, 9, 10, 13, and 14 of Group 2 aorta was examined. In Case 2 mild atherosclerosis was shown. Case 3 had no significant changes in the aorta. In the cases examined of Group 2 all had moderate to advanced atherosclerosis of aorta. Associated with atherosclerotic changes were sclerosis and scarring of subjacent media which were found in Cases 7, 10, and 14. In Case 14 some sclerosis of adventitia was also seen. Case 7 demonstrated slight intimal sclerosis and hypertrophy of myofibers of media of the arterioles of vasa vasorum. In Cases 10 and 14 mild to moderate sclerosis of intima of the arterioles of adventitia and external layer of media was recognizable.

General Considerations and Discussions

The pathologic processes presented here were in detail comparable to various pathological changes occurring in arterial trees including capillaries of organ tissues which had been described by Schürmann and MacMahon (1933). Throughout the own observations of the present author it was also revealed that alterations of arterioles and small arteries as well as organ tissues were most intense and extensive in kidneys among various organs.

Granuloma formation surrounding the area of arteriolonecrosis which had been pointed out by Fahr (1925), Klemperer and Otani (1931), and Schürmann and MacMahon (1933) was not encountered in the present study just as Heptinstall (1974) had stated that the lesion is usually a necrosis without inflammatory cells. Intimal hyperplasia of arterioles and small arteries originally called productive endarteritis by Fahr (1925) has been believed to be one of the characteristic vascular lesions in malignant nephrosclerosis. In agreement with Klemperer and Otani (1931) and Schürmann and MacMahon (1933) who gave more detailed descriptions of the lesion, the present author noticed intimal thickening with proliferation of reticular or spindle-shaped cells connected with their cytoplasmic processes and not infrequently associated with basophilic mucoid swelling of intercellular tissue (intimal cellular hyperplasia), which was most frequently seen in interlobular arteries and occasionally in arcuate arteries. It was revealed by sequential study employing renal biopsy and following autopsy in Case 14 that the lesion was followed by concentric fibrous thickening (concentric fibrosis) of intima. The latter lesion was only encountered in a few cases of Group 2. These intimal lesions were visible in follicular arteries and capsular arterioles of adrenals in some cases. Perinuclear vacuolization of myofibers of media, which had been thought to be a manifestation of vascular contraction by Takeuchi (1974), was most frequently shown in inter-
lobular arteries of kidneys, less frequently in arcuate arteries, and occasionally in interlobar arteries, arterioles and branches of coronary arteries, arterioles and small arteries of pancreas, arterioles of brain, arterioles and small arteries of digestive tract, interlobular arteries of liver, and capsular arterioles of adrenals.

A kind of glomerulitis characterized by nuclear increase and epithelial hyaline droplet degeneration has been described by Fahr (1925), Klemperer and Otani (1931), Schürmann and MacMahon (1933), Lüders (1951), and Zollinger (1961), and the lesion has been interpreted to be related to renal insufficiency (Fahr 1925) or thought to be of ischemic nature (Klemperer and Otani 1931). But, the present author prefers to understand that such a glomerular lesion is comparable in its histogenesis to that of intimal cellular hyperplasia of interlobular arteries and so on as mentioned above, and interprets that the lesion is due to ischemia caused by stenotic changes of the proximal segments of arterioles. Development of “endocrine kidney” structure which was originally observed and called by Selye and Stone (1946) in the kidneys experimentally rendered ischemic by aortic ligation between the origins of bilateral renal arteries was noted in the present study especially in cases of Group 2. In contrast to Selye and Stone (1946) and Heptinstall (1974) considering the structure to be derived from proximal convoluted tubules, the author prefers to agree with Bohle (1954) who had stated that such a structure comes from distal convoluted tubules, because the “endocrine kidney” structure in cases presented here was provided with capillary networks accompanied by little connective tissue, which was not consistent with advanced atrophy and sclerosis of proximal convoluted tubular tissue but with comparatively well preserved distal convoluted tubular tissue. Hyperplasia of juxtaglomerular cells, which had been pointed out by Jones (1953) as a rarely occurring change in malignant nephrosclerosis and described by Bohle et al. (1973) in a case of secondary malignant nephrosclerosis, was recognized in 2 cases of Group 2. Marked stenosis of interlobular and arcuate arteries in these cases appeared related to the hyperplasia.

Difference between histologic manifestations of pure and exacerbated forms of malignant nephrosclerosis

As already mentioned, little information of the difference between histologic manifestations of pure and exacerbated forms of malignant nephrosclerosis has been available so far.

The present study revealed that hyalinization of glomeruli, swelling and thickening of glomerular loop walls with cellular increases and hyaline droplet degeneration of glomerular epithelial cells, compensatory hypertrophy of renal tissue, and “endocrine kidney” structure were more frequently visible in the exacerbated form (Group 2) than in the pure form (Group 1), and thickening of capsular walls was encountered only in Group 2, whereas epithelial crescent formation appeared more often in Group 1 than in Group 2. Anemic infarction of kidney was seen in Group 1, while moderate hyperplasia of juxtaglomerular cells was found only in Group 2. Complication of pyelonephritis was more frequent in
Group 2 than in Group 1. Concerning the vascular lesions, the pure form of malignant nephrosclerosis was characterized by edema or histolysis of intima of interlobular, arcuate, and interlobar arteries; hyaline degeneration of afferent arterioles; intimal cellular hyperplasia of interlobular and arcuate arteries; hemorrhage into intima of afferent arterioles, and interlobular and arcuate arteries; fibrinoid necrosis of afferent arterioles and distal segments of interlobular arteries; and, hypertrophy and hyperplasia of myofibers of media of interlobular, arcuate, and interlobar arteries. On the contrary, the exacerbated form characteristically had sclerosis of intima of interlobular, arcuate, and interlobar arteries; lamellar elastosis of interlobular, arcuate, and interlobar arteries; intimal cellular hyperplasia or concentric fibrosis of intima of interlobular arteries; intimal cellular hyperplasia which occurred in the luminal side of sclerotic intima or in the inside of intima showing lamellar elastosis of interlobular arteries; hemorrhage into intima of afferent arterioles and interlobular arteries; hemorrhage into intima with cellular hyperplasia of interlobular arteries; hemorrhage into intima with concentric fibrosis of interlobular arteries; fibrinoid necrosis of sclerotic intima of distal segments of interlobular arteries; fibrinoid necrosis of intima with cellular hyperplasia of distal segments of interlobular arteries; perinuclear vacuolization of myofibers of media of interlobular and arcuate arteries; decrease in numbers of myofibers and interstitial sclerosis of media of interlobular and arcuate arteries; and, occasional atherosclerosis of interlobular arteries. Arterioles and small arteries of heart, spleen, liver, pancreas, adrenals, digestive tract, brain, and aorta had histologic changes similar to those mentioned above, but the lesions were generally much milder than those of kidneys.

Among the lesions mentioned above, concentric fibrosis of intima, intimal cellular hyperplasia in the luminal side of sclerotic intima or in the inside of intima showing lamellar elastosis, hemorrhage into intima with cellular hyperplasia, hemorrhage into intima with concentric fibrosis, and fibrinoid necrosis of sclerotic intima of interlobular arteries were recognized only in the exacerbated form, while fibrinoid necrosis of intima with cellular hyperplasia of distal segments of interlobular arteries was more frequently seen in the exacerbated form than in the pure form. In 2 or 3 cases of the exacerbated form, it was also noted that coexistence of hemorrhage into intima, hemorrhage into intima with cellular hyperplasia, and hemorrhage into intima with concentric fibrosis, or that of fibrinoid necrosis of not thickened intima, fibrinoid necrosis of sclerotic intima, and fibrinoid necrosis of intima with cellular hyperplasia appeared in the same kidneys. In 4 cases of the exacerbated form, concurrence of intimal cellular hyperplasia, intimal concentric fibrosis, and intimal cellular hyperplasia in the luminal side of sclerotic intima or in the inside of intima with lamellar elastosis was observed.

Do these histologic manifestations mean mere coexistences of mutually unrelated lesions or superpositions of one on the other? Schürmann and MacMahon (1933) pointed out that not infrequently associated with fibrinoid necrosis
was lysis of subendothelial ground substance or its successive change, which was
the case more often in small arteries than in arterioles. Bohle et al. (1973)
described partial hemorrhage into intima with productive endarteritis (examples 1
and 3 of secondary malignant nephrosclerosis), productive endarteritis with fibrinoid
necrosis of intima (example 2 of secondary malignant nephrosclerosis), and stenotic
intimal edema followed by collagenous productive endarteritis with subendo-
thelial fibrinoid necrosis of interlobular arteries 193 days later (example 4 of
primary malignant nephrosclerosis), obstructive lesion of interlobular arteries
characterized by collagenous tissue hyperplasia having hemosiderosis which was
recognized in the kidneys resected 84 days after the onset of the disease (example
3 of primary malignant nephrosclerosis). But, these authors did not refer to the
significance of these lesions. In Case 14 of the exacerbated form sequential study
by renal biopsy and autopsy 47 days later revealed an occurrence of fibrinoid
necrosis in the subendothelial layer of intima of distal segments of interlobular
arteries which had been already sclerotic. Fujimoto et al. (1967) also pointed out
similar lesions in the contralateral kidney when an exacerbation with malignant
hypertension appeared in the course of renovascular hypertension. Among the
histological changes here in question, sclerosis and lamellar elastosis of intima of
interlobular arteries usually accepted as consistent with benign nephrosclerosis were
more frequently and intensely seen in the exacerbated form than in the pure form.
These changes are considered to be rather static and advanced or old in nature.
Intimal cellular hyperplasia first noticed in malignant nephrosclerosis and named
productive endarteritis by Fahr (1925) was more frequent and intense in the
exacerbated form than in the pure form. Schüermann and MacMahon (1933) also
noticed the development of occasional productive endarteritis in 2 cases of benign
nephrosclerosis with renal decompensation. It was also revealed in the present
study that the intimal cellular hyperplasia was later followed by intimal concentric
fibrosis. Therefore, intimal cellular hyperplasia appears more dynamic and
shorter in duration than sclerosis or lamellar elastosis of intima. In contrast to
these lesions, fibrinoid necrosis and hemorrhage into intima are interpreted to be
acute or recent lesions, and when combined with sclerosis or cellular hyperplasia of
intima fibrinoid necrosis occurred in the subendothelial layer or in the external
layer of thickened intima adjacent to media. Intimal cellular hyperplasia coexistent
with either sclerosis or lamellar elastosis of intima also appeared in the luminal
side or in the inside of thickened intima. Accordingly, intimal cellular hyperplasia
in the luminal side of sclerotic intima or in the inside of intima with lamellar
elastosis, hemorrhage into intima with cellular hyperplasia or into intima with
concentric fibrosis, and fibrinoid necrosis of sclerotic intima or of intima with
cellular hyperplasia are not necessarily specific for exacerbated form, but they are
histologic manifestations of recurrence which is the case more frequently in
exacerbated form than in pure form in the longer course of essential hypertension or
of malignant hypertension (Fig. 17).
Zollinger (1951) noted that secondary occurrence of arteriolonecrosis in the younger patients with chronic glomerulonephritis was more frequently seen than that in the aged patients, and considered this is due to the loose property of vascular walls in younger patients. However, age difference in fibrinoid necrosis was not significant in the present study so far as the observation of 14 patients between the ages of 24 and 62 years was concerned. From the present study it was suggested that difference of histologic manifestations is more dependent on the acquired properties of vascular walls than on the ages of patients alone. Heptinstall (1953) stated that the main difference in the kidneys in cases of essential hypertension in the benign and malignant phases respectively is that in the latter vascular necrosis appears and runs parallel to the height of the blood pressures. Such a parallel relationship between the intensity and frequency of fibrinoid necrosis of arterioles and small arteries and the height of blood pressure was not clearly ascertained in the present study. McCormack et al. (1958) studied the influence of anti-hypertensive therapy upon arteriolar and arterial lesions, which was characterized by remission and healing of acute arteriolar thrombosis, thrombosis, and glomerular necrosis, and subintimal fibroplasia of larger and medium-sized arteries with progression to occlusion. Harington et al. (1959) reported a conversion of cellular intimal hyperplasia in the interlobular arteries to fibrous intimal thickening, and a “healing” of fibrinoid degeneration to hyaline and fibrous tissue observed in 42 autopsied patients of malignant hypertension treated with hypotensive drugs over periods varying from one week to two years. In the present study 5 cases were treated with anti-hypertensive drugs, in 2 cases of which there were some improvements in the symptoms, whereas the others showed no responses. The two cases with some improvements demonstrated neither fibrinoid necrosis of afferent arterioles nor intimal cellular hyperplasia of distal segments of interlobular arteries, though one of the two cases showed concentric fibrosis of intima and hemorrhage into intima of distal segments of interlobular arteries, and the other had fibrinoid necrosis of distal segments and hemorrhage into intima of proximal segments of interlobular arteries.

Relation between essential hypertension and malignant nephrosclerosis

As aforementioned, Schürmann and MacMahon (1933) classified malignant nephrosclerosis into two forms, genuine from developing from essential hypertension and exogenous-toxic form with acute onset of disease. The former had been believed to be an essential feature of malignant nephrosclerosis by Volhard (1931) and the latter by Fahr (1925). Recently, Bohle et al. (1973) divided this disease into primary and secondary malignant nephrosclerosis. The primary malignant nephrosclerosis seems to be almost corresponding to the exogenous-toxic form of Schürmann and MacMahon, whereas the secondary malignant nephrosclerosis corresponds to the genuine form of Schürmann and MacMahon. It was notable that Bohle et al. reported an occurrence of primary malignant nephrosclerosis with no or slight elevation of blood pressure in 5 out of 22 cases. In the 14 cases of malignant nephrosclerosis presented here, however, cases without clinically
demonstrable elevation of blood pressures at the onset of symptoms or at the time of exacerbation were not included. The author classified malignant nephrosclerosis into pure form in which syndrome of malignant hypertension developed from the beginning of the disease, and exacerbated form in which exacerbation due to appearance of the syndrome occurred in the course of essential hypertension. In the exacerbated form sclerosis and lamellar elastosis of small arteries and arterioles usually accepted as consistent with benign nephrosclerosis were frequently and extensively recognized, and intimal cellular hyperplasia in the luminal side of sclerotic intima or in the inside of intima with lamellar elastosis, hemorrhage into intima with cellular hyperplasia or into intima with concentric fibrosis, fibrinoid necrosis of sclerotic intima or of intima with cellular hyperplasia were seen in addition to intimal cellular hyperplasia, hemorrhage into not thickened intima, and fibrinoid necrosis usually appearing in the pure form. It is probable from these facts that malignant nephrosclerosis superimposed on benign nephrosclerosis develops as an exacerbation with syndrome of malignant hypertension in the course of essential hypertension. The pure form suggests acute onset of malignant nephrosclerosis without any notable period of ease only associated with hypertension prior to appearance of syndrome of malignant hypertension. Through the histological characteristics especially those of acute lesions demonstrated in the two forms, the mechanisms involved in the pathogenesis of arteriolar and arterial changes appear to be common to the pure and exacerbated forms. Irrespective of the forms it is highly probable that the patients are susceptible to recurrence in the course of disease, which makes the pathologic features more complicated. Elucidation of the mechanisms awaits further studies.

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References