Pathological Study on Development of Chronic Glomerulonephritis

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For the study of chronicity, malignancy or development of diffuse glomerulonephritis, 60 autopsy cases of chronic glomerulonephritis were selected and their intrarenal vascular changes were compared with respective clinical data and clinical course.

In arteries measuring over 200µ in diameter, the degree of arteriosclerosis was totally proportional to age, duration of illness, blood pressure, etc., and the degree of fibrous simple thickening, fibrous proliferative thickening and necrosis was proportional to duration of illness but not necessary to other factors.

As to histological findings, glomerular changes were in proportion to vascular changes in intensity. Malignant phase of chronic glomerulonephritis was noted in 20 cases and in most of these cases the duration of illness from onset of nephritis to death was relatively long. Such malignant cases rapidly increased in number since 1963 and there were noted some cases of death due to cerebral vascular insufficiency.

INTRODUCTION

Concerning diffuse glomerulonephritis, many studies have been carried out beginning with the presentation of BRIGHT’s disease in 182743 and including VOLHARD’s classification in 193128). Moreover, due to the rapid progress of renal function tests9) and application of percutaneous renal biopsy11211), sectioning, staining12213), electronmicroscopes 222233 and immunological methods561518) in recent years, observation has been made from new-aspects and new knowledge is being added to the conventional understanding. On the other hand, concerning the relationship between the kidney and hypertension, many studies have been made on juxta glomerular apparatus, renin-angiotensin system, 31426 etc., and fairly good results are being obtained. Despite those efforts, however, many important factors still remain unknown. The
matter of chronicity as well as malignancy of chronic glomerulonephritis is an example of unknown problems. In consideration of the fact that hypertension is believed to be one of the factors of chronicity or malignancy of glomerulonephritis, a study was made by the author on the relationship between the two from standpoint of histological changes especially on arteriolar and arterial changes and in comparison with the clinical course or clinical data.

MATERIALS AND METHODS

Of the 4816 autopsy cases handled by the Department of Pathology, Nagasaki University School of Medicine, from 1948 to 1965, 60 cases (1.2%) with definite diagnosis of chronic glomerulonephritis were selected as the sample of this study. The diagnosis of chronic glomerulonephritis was made in distinction from "malignant phase" of essential hypertension in histological consideration of the diffused distribution of glomeralar changes and proliferative changes of glomerular cells and in reference with the clinical course especially with the symptoms of glomerulonephritis at onset.

Questionable cases and those with insufficient clinical data were excluded from the sample. Chronological change: Among the 60 cases of sample, incidence of glomerulonephritis increased annually along with the increase of total autopsy cases. The trend has been remarkable since 1962 (See Fig. 1).

![Fig. 1 Cases of chronic glomerulonephritis and total autopsy cases](image-url)
Fig. 2 Cases of chronic glomerulonephritis and age

Age distribution: The age at death is 33 years and 4 months in average ranging from 3 years and 1 month to 68 years and 10 months. Except for the under 10 and over 50, age distribution is approximately uniform even though date was somewhat high in the age group of 20's. (Fig. 2).

Sex distribution: There were 42 cases in male and 18 cases in female. The ratio of male to female was 7:3. Clinical course:
1) Acute glomerulonephritis was experienced (ELLIS’ type I) by 20 cases (33.3%) and not experienced (ELLIS’ type II) by 40 cases (66.7%)
2) Nephrotic syndrome was experienced during the course by 9 cases 8 cases of type I nephritis and 1 case of type II nephritis.
3) Blood pressure was normal in 10 cases but hypertensive in all other cases.
4) Duration of illness or the period from onset to death varied from a minimum of 20 days to a maximum of 34 years with the average of 4 years and 8 months.
5) Cause of death: Though it is somewhat dangerous to deter-

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Comparison of type I and type II nephritis</th>
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<tr>
<td></td>
<td>Cases</td>
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<tr>
<td>I type</td>
<td>20</td>
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<td>(33.3%)</td>
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<td>II type</td>
<td>40</td>
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<td>(66.7%)</td>
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<td>Total or Average</td>
<td>60</td>
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Table 2  Macroscopically visible cerebral accidents

<table>
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<tr>
<th>Cerebral accidents</th>
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<tr>
<td>Cerebral hemorrhage</td>
<td>2 cases</td>
</tr>
<tr>
<td>Encephalomalacia</td>
<td>4 cases</td>
</tr>
<tr>
<td>Subarachnoid hemorrhage</td>
<td>3 cases</td>
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<tr>
<td>Uremic petechial hemorrhage</td>
<td>3 cases</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>11 cases</strong> (among 39 cases)</td>
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mine the immediate cause of death only from the clinical history and pathological findings, most of the cases died of uremia. Other possible causes of death for 39 cases with which intracranial study was made so-called "hypertensive cerebral hemorrhage" in 2 cases, encephalomalacia in 4 cases, subarachnoid hemorrhage in 3 cases, and uremic petechial hemorrhage in 3 cases. Besides these, hypertensive cardiac failure was noted in 2 cases and complication of bacterial pneumonia in 4 cases. The above is summarized in Table 1 and 2.

For preparation of histological specimens, the kidneys including cortex and medulla fixed by 10% formalin solution were made into sections measuring 3 cm² or more in size, embedded in paraffin, sliced to be about 4μ in thickness, and stained by hematoxylin-eosin, Weigert’s elastica stain, van Gieson stain, PAS stain, PAM stain and Mallory-Azan stain.

In determination of vascular changes, intrarenal arterioles were classified into small arterioles measuring less than 200μ in diameter and larger arteries measuring more than 200μ in diameter and 100 pieces of former and 20 pieces of the latter were selected for each of the right and left kidneys, and the total of vascular changes in each artery or arteriole was determined as 0— +3. As to glomerular changes, 50 glomeruli were selected for each of the right and left kidneys and the total of glomerular changes in each glomerulus was determined as 0 — +3.

**RESULTS**

A. Histological changes on arterioles (<200μ).

Among the cases of chronic glomerulonephritis that were autopsied, there was no case without any vascular change, except for the cases that died at an early stage due to complication. Moreover, vascular changes were fairly advanced in the cases with hypertension. Most remarkable changes were noted on arterioles especially in afferent arterioles and ampulla portion of glomerular capillary.

(1) Fibrous simple thickening.

This is a representative arteriolar change in the cases of benign hypertension. Hyalineous or fibrous thickening was noted evenly throu-
through the arteriolar wall (photo. 1). Changes in endothelial cells were hardly observed. Fibrous simple thickening was noted in various degrees in all the cases including normotensive cases but excluding the cases of short duration of illness and early death due to complication.

(2) Fibrous proliferative thickening.

As compared with fibrous simple thickening, hyalinous changes were poor, the arteriolar wall was evidently thickened fibrously and the myofiber were proliferated resulting in the narrowing of the arteriolar cavity which resemble the findings of onionskin lesion observed in systemic lupus erythematosus (photo. 2). Such changes are regarded by some investigators to be fibrous simple thickening. However, the author dared handle these separately and compared these with other data.

(3) Necrosis.

There was noted so-called "fibrinoid necrosis" involving materials which were homogenously swollen on the entire circumference of the arteriolar wall and stained deeply by PAS stain. There was another type of change in the subintimal space involving materials which were stained deeply by eosin and PAS positive. This type of change is believed to be the initial stage of the former. These two types of change were described as necrosis (photo. 3, 4 and 5).

(4) Angitis.

In addition to the above three arteriolar changes, angitis was a peculiar finding though the incidence was rare. In the afferent arterioles of two cases (one age 68 years and 10 months and the other age 37 years and 9 months) the cells of the wall around fibrinoid necrosis were proliferated outwards in nodular shape. Infiltrated cells were also noted in the region (photo. 6).

B. Histological changes on larger arteries (>200μ).

On larger arteries in the renal parenchyma measuring over 200μ in diameter, intimal thickening and elastosis in various degrees were generally noted. In other words, usual arteriosclerosis was the only finding and there was no necrosis nor angitis (photo. 7).

C. Change in ampulla portion of glomerular capillary.

In addition to the vascular changes, degenerative changes of glomeruli and extracapillary proliferative change previously stated in cases with chronic glomerulonephritis, changes in ampullar portion of glomerular capillary should not be overlooked. The changes were thickening of the wall, narrowing of the internal cavity due to cell proliferation (photo. 9), dilatation, infiltration of serum components (photo. 11), hemorrhage, thrombosis (photo. 10) and angitis accompanied with fibrinoid necrosis distributed diffusely on the afferent arterioles (photo. 6). As the changes in the ampullar portion increased in intensity, the
changes in the peripheral area of glomerular tufts were also intensified resulting in hemorrhage, thrombosis, necrosis and crescent. Such changes are the findings often observed in "malignant type" which is described below.

D. Malignant phase of chronic glomerulonephritis\(^8\) (malignant type).

The above-stated arteriolar glomerular changes such as necrosis, angitis and proliferative glomerulitis are the findings of so-called "ma-

<table>
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<th>Table 3 Malignant phase of chronic glomerulonephritis</th>
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<tr>
<td>No. of autopsy</td>
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<tr>
<td>3877*</td>
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<td>5374</td>
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<td>7366</td>
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<td>7701</td>
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<td>Average</td>
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Non-malignant type

| Average        | 29y10m | 3y | 160/ 90         | +1.6            +0.5          +1.0                   | +0.9              +0.2          +0.8                   |

Total

| Average        | 33y4m | 4y8m | 176/105         | +1.8            +1.0          +1.2                   | +1.2              +0.6          +1.1                   |

*type I nephritis
lignant nephrosclerosis" itself. Further, cases having remarkable cardiac or cerebral symptom are regarded as "malignant phase of chronic glomerulonephritis".

Among the 60 cases of sample, malignant type was observed in 20 cases. As shown in Table 3, male-female ratio was about 2:1. In comparison with the ratio of 7:3 in total cases, incidence of malignant type is high in females. The age at death, duration of illness, blood pressure and histologic findings were all higher in degree in malignant type than in non-malignant type. As to vascular changes, not only necrosis and fibrous proliferative thickening but also fibrous simple thickening and arteriosclerosis were more advanced in most cases of malignant type (Table 3). Moreover, the stronger were the vascular changes, the more advanced were glomerular changes especially extracapillary changes in most cases. However the degree of these changes was not necessarily in parallel with the blood pressure.

Chronologically, malignant type showed a trend of rapid increase after 1963 as shown Fig. 1.

E. Comparison between vascular changes and clinical course.

The relationship between vascular changes and each of age, duration of illness and blood pressure was investigated in all cases.

Age: An apparent correlation was noted between arteriosclerosis of larger arteries (>200μ) and age, but advanced (+1 or more) fibrous simple thickening, necrosis and fibrous proliferative thickening showed no correlation with age though many cases in younger group had no such vascular change. Fibrous simple thickening 0 was noted only in two young cases who died at an early stage due to complication. There were some cases of fairly advanced age that were absolutely free from necrosis and fibrous proliferative thickening. In other words, the changes in small arterioles measuring less than 200μ had no relation with age. Most cases of malignant type showed changes of +2 more (Fig. 3).

Duration of illness: Irrespective of the size of arteries and nature of changes, there was a close correlation between all vascular changes and duration of illness, i.e. the longer was duration, the more advanced were the vascular changes. Particularly in small arteriolar changes (fibrous simple thickening, necrosis and fibrous proliferative thickening), the patterns of +2 and +3 were totally reversed as compared with Fig. 3 (Fig. 4).

Blood pressure: Each vascular change was almost parallel with blood pressure both systolic and diastolic. However, as shown in Fig. 5, fibrous simple thickening and arteriosclerosis (>200μ), and necrosis and fibrous proliferative thickening respectively showed a similar pattern. While in the former group the blood pressure was in complete correlation with the degree of vascular change, the latter group showed
Fig. 3 Vascular changes and age

- Fibrous simple thickening
- Necrosis
- Fibrous proliferative thickening
- Arteriosclerosis (> 200μ)

- malignant type
- non-malignant
- average

Fig. 4 Vascular changes and duration of illness

- Fibrous simple thickening
- Necrosis
- Fibrous proliferative thickening
- Arteriosclerosis (> 200μ)
a decrease of blood pressure as the vascular change increased from +2 to +3. Blood pressure over 200 mmHg was frequent in cases with +2 and +3 of fibrous simple thickening and arteriosclerosis (>200μ) but in cases with +1 and +2 of necrosis and fibrous proliferative thickening.

From this point of view, vascular changes may be classified into following 3 groups: 1) arteriosclerosis (>200μ) which is closely related to age and blood pressure, 2) fibrous simple thickening which is related only to blood pressure, and 3) necrosis and fibrous proliferative thickening which are little related to either factor.

DISCUSSION

As the causes of chronicity and malignancy of diffuse glomerulonephritis, many factors have been indicated by investigators, such as the degree of attack at onset, intrinsic progress of renal changes, continuation of the primary lesion or reinfection, inadequate care of patient, family factor and also development or extension of vascular changes.

The author paid attention to hypertension and vascular changes and compared them with clinical course and other factors in 60 autopsy cases,
Clinical course: The 60 autopsy cases were classified according to Ellis' classification into 20 cases (33.3%) of type I nephritis, and 40 cases (66.7%) of type II nephritis. Generally type I nephritis is believed to be relatively well curable with satisfactory prognosis. In the present study, autopsy cases of type I nephritis occupied 1/3 of the total cases, which is not so rare. However, it was reported by Sarre that acute nephritis with nephrotic syndrome results in poor prognosis. Of the 20 cases of type I nephritis in the present study, 8 cases (40%) indicated nephrotic syndrome during the course, and it is not contradictory that type I nephritis indicated relatively high percent of the total cases. In the group of type II nephritis, only 1 case (2.5%) showed nephrotic syndrome.

In comparison with type II nephritis was longer in duration of illness but lower in age at death, onset being seen in young subjects. These findings were in conformity with many other reports.

Concerning blood pressure, there was a great difference between type I and type II. The difference was 10 mmHg in diastolic pressure and 30 mmHg in systolic pressure. Since type II nephritis is often accompanied with hypertension from the onset, the difference between two types is understandable.

However, as to the difference between systolic and diastolic pressure, the author has no answer at present. Intracranial changes were of course more frequent in the cases of type II nephritis which were often accompanied with intensive hypertension.

Arterial changes: Arteriosclerosis in the arteries measuring over 200μ showed correlation with age. Arteriosclerosis in the arterioles measuring under 200μ and fibrous simple thickening had correlation with blood pressure as reported by other investigators. However, necrosis and fibrous proliferative thickening, had no correlation with age, and cases with +3 degree of there vascular changes indicated evidently lower valve of blood pressure than cases with +2 degree.

All these arterial and arteriolar changes showed a close correlation with duration of illness. This evidence suggests that the vascular changes are not simply due to age and blood pressure but rather affected by the continuation of nephritis.

Among various arteriolar changes in chronic glomerulonephritis, fibrous proliferative thickening which is rare in other organs and observed mostly in the arterioles measuring under 200μ was given a special consideration in this study. In the past fibrous proliferative thickening had been regarded as arteriosclerosis in the same light with fibrous simple thickening. On the other hand, this was considered by Bell and Clauson, Murphy and Gill, and Huckel as a characteristic change of malignant nephrosclerosis and described as "concentric arteriolitis". The author can not agree that fibrous proliferative...
thickening is regarded simply as arteriosclerosis in the same light with fibrous simple thickening, and moreover, the expression of arteriolitis is not adequate since this type of thickening is entirely different morphologically from periarteritis or panarteritis. The various data of fibrous proliferative thickening described above shows the same pattern as necrosis rather than arteriosclerosis (>200μ) or fibrous simple thickening. It is deemed from the above that fibrous proliferative thickening is not a mere sclerotic change but a peculiar change with some potentiality in itself and/or in "nephritic ground and environment".

Malignant phase of chronic glomerulonephritis:

Recently, cases with clinical symptoms of chronic glomerulonephritis accompanied with malignant hypertension and remarkable cardiac and cerebral disorders who would finally die of uremia have drawn attention of those concerned as malignant phase of chronic glomerulonephritis in comparison with malignant phase of essential hypertension. In this study, the author selected among 60 cases of sample 20 cases with the above-stated clinical symptoms and histological findings of so-called "malignant nephrosclerosis". The results of study in this aspect may be summarized as follows.

1) There were 13 male cases and 7 female cases. The rate of female cases was higher than in total cases. (2) Type I nephritis was noted in 4 cases and type II nephritis in 16 cases. (3) In comparison with non-malignant group, age at death was higher by 10 years and 6 months. (4) The duration of illness was over twice as long as that in non-malignant group. (5) Blood pressure and histologic findings were greatly different from those in non-malignant group. (6) Cases of malignant type have rapidly increase since 1963.

Whereas the mean value of the duration of type II nephritis was extremely shorter than that of type I nephritis the duration of the malignant type with included mainly type II nephritis was twice longer. This indicates that a long duration of the nephritis may be an important factor development of malignant type and the rapid increase of the cases of malignant type since 1963 may be due mostly to the longevity effect of the therapies, such as rest in early stage, treatment against the primary lesion and complication, and administration of depressor drugs, diuretica, adrenal cortical hormone and so forth. However, the data of the author failed to show any special evidence to support this presumption.

In conclusion, the author emphasized that so-called "malignant type" appears during the course of chronic glomerulonephritis due to advanced arteriolar changes and that cases of death due to cerebral accident particular cerebral hemorrhage had been increasing.
SUMMARY

With 60 autopsy cases of chronic glomerulonephritis, histological findings of the kidney, particularly intrarenal arterial and arteriolar changes were compared with clinical course.

The arteries were classified by diameter into those over 200μ and those under 200μ. Whereas the former showed only usual arteriosclerosis, the latter demonstrated fibrous simple thickening, fibrous proliferative thickening, necrosis and angitis, though the last one was noted only in 2 cases.

The degree of vascular changes was compared with clinical data such as age, duration of illness and blood pressure. Arteriosclerosis of larger arteries (>200μ) was proportional to age. On the contrary, all vascular changes were totally proportional to duration of illness. Grade of both fibrous simple thickening and arteriosclerosis (>200μ) was parallel to blood pressure. On the contrary grade of both fibrous proliferative thickening and necrosis was proportional to blood pressure, i.e. Cases having high degree vascular changes showed rather lower blood pressure.

The author considered fibrous proliferative thickening not simply as a sclerotic change but as a change close to necrosis or angitis.

Malignant phase of chronic glomerulonephritis was noted in 20 cases (33.3%), 16 of which were of type II nephritis. In comparison with non-malignant type, malignant cases showed higher values in blood pressure and higher degree of histological vascular changes, and moreover they were higher in age by 10 years and 6 months and longer in duration of illness by 4 years and 2 months. Malignant phase of chronic glomerulonephritis rapidly increased in incidence since 1963.

In view of the above, it is indicated that the patients of chronic glomerulonephritis may survive longer due to the advancement of treatment and rehabilitation, and accordingly it may be anticipated that hypertension and more intensive vascular changes would develop resulting in more cases of death due to cerebral vascular insufficiency such as cerebral hemorrhage.

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DEVELOPMENT OF CHRONIC GLOMERULONEPHRITIS

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Photo. 1 fibrous simple thickening, H-E stain (10×40)

Photo. 2 fibrous proliferative thickening, H-E stain (10×16)

Photo. 3 subintimal necrosis, H-E stain (10×40)
Photo. 4 fibrinoid necrosis, PAS stain (10×40)

Photo. 5 fibrinoid necrosis, PAS stain (10×40)

Photo. 6 angitis, H-E stain (10×16)
Photo 7: Arteriosclerosis (>200μ), H&E stain (10×16)

Photo 8: Fibrinoid necrosis of afferent arteriole and hyaline droplet in glomerular tuft. H&E stain (10×16)

Photo 9: Thickening, cell proliferation and narrowing in ampullar portion of glomerular capillary
Photo. 10  hemorrhage and early stage of thrombosis in ampullar portion of glomerular capillary

Photo. 11  dilatation and infiltration of serum component in ampullar portion of glomerular capillary.

Photo. 12  proliferation of capsular and glomerular cells.