Perivascular and interstitial fibrosis in the kidney associated with liver cirrhosis: A histopathologic study of autopsy cases

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Key words: liver cirrhosis, interstitial fibrosis, perivascular fibrosis, renal circulation, pyelonephritis

Abstract

Among the renal lesions associated with hepatic disorders, glomerular changes in cases of liver cirrhosis (L.C.) have been extensively studied by many investigators. On the other hand, from the standpoint of clinical medicine, Epstein et al. reported renal circulatory disturbances in L.C. from a selective renal angiogram obtained in a patient with oliguric renal failure.

In this study, the author therefore attempted to identify histological abnormalities causing such circulatory disturbances by examining autopsied kidneys of L.C., and compared the results obtained with those of pyelonephritis which served as a control. As a result, 80% of L.C. was found to show perivascular and diffuse interstitial fibrosis of the renal medullae as demonstrated by Elastica-Van Gieson stain which could be identified very easily with either the naked eye or the aid of a hand lens. Such interstitial fibrosis in L.C. was especially significant in the perivascular region and involved the so-called venous muscular complex proposed by Takeuchi.

The renal circulatory disturbances associated with L.C. proposed by Epstein appeared to be well supported by the present results if the venous muscular complex around the renal venous system has the ability to squeeze out blood towards the vena cava, since the fibrosis involving this complex, accordingly, caused significant impairment to the renal circulation. In this respects, the results also cast some light on the mechanisms of the renal circulation.

Introduction

Among the renal lesions associated with hepatic disorders, glomerular changes by liver cirrhosis (L.C.) have been extensively studied by many investigators. In 1959, Bloodworth and Sommers [1] proposed the term “cirrhotic glomerulosclerosis” and suggested a scheme for grading such sclerosis. On the other hand, in 1970, from the standpoint of clinical medicine, Epstein et al. [2] reported the existence of circulatory disturbances in the kidney in L.C. based on a selective renal angiogram obtained in a patient with oliguric renal failure and L.C. They demonstrated severe abnormality of the intrarenal vasculature, including the interlobular arteries off the main renal arteries with unrecognizable more peripheral arteries when the patient was alive. A postmortem angiogram of the same kidney, however, had lost such abnormality according to them. They reported that the blood vessels were histologically normal, and claimed that to be evidence for the functional basis of renal failure operating through renal vasoconstriction. This report influenced investigators so strongly that it was introduced in a standard textbook on medicine in Japan [3].

Our recent brief study [4] of autopsied kidneys in cases of L.C. also suggested the presence of marked circulatory disturbances in the postglomerular region based on strong dilatation of the vascular pole and capillaries of the glomeruli as in the postglomerular vasculature. Interstitial capillary engorgement was regarded by Bohle et al. [5] as a sign of de-
creased blood supply causing ischemic injury to endothelial cells of the intertubular capillaries leading to interstitial edema and later fibrosis. The present author therefore attempted to identify histological abnormalities causing such postglomerular circulatory disturbances which are presumed to occur either in the vascular system or in the interstitium of the kidney in cases of L.C.

Materials and Methods

Autopsy cases of L.C. from the past 10 years at Kyorin University and its affiliated hospitals formed the subjects of the present study. Cases combined with diabetic nephropathy, acute tubular necrosis, primary and metastatic tumors in the kidneys, and pyelonephritis, were not included in the total of 25 cases studied. For histologic examinations, formalin-fixed and paraffin embedded livers and kidneys were selected from the files of routinely processed tissue blocks. The tissue sections were stained with hematoxylin and eosin, periodic acid Schiff (PAS), colloidal iron and PAS, and Elastica-Van Gieson (El-VG) stains. L.C. was classified into Nagayo’s type A and type B [6]. For grading of the interstitial changes in the kidneys, the author proposed her own criteria (Figs. 1 to 4). This classification was best done by hand lens observation of the kidney sections with El-VG stain. Grade 0 was given to the findings of cases in which no significant fibrosis was observed in any part of the kidney (Figs. 1 and 2), although some red coloration around the vasculature could be present. In grade 1, fibrosis characterized by red staining of the interstitium by El-VG stain was observed in the renal medulla, but not in the cortex, accompanied by a more intense red coloration of the vascular system especially in the interlobar and arcuate veins (Figs. 1 and 3). In grade 2, in addition to the findings of grade 1, the fibrosis extended towards the cortex, as well as occurring in the medulla, and the red coloration of the vasculature was even more distinct than in cases of grade 1 (Fig. 4; cf. Fig. 3). The creatinine levels in most cases evaluated within the last hospitalization were compared with the degree of proposed renal fibrosis. The relative proportions of cases showing each grade of fibrosis and type of cirrhosis were also assessed. These features of the interstitial changes were compared with those of 31 autopsy cases including acute and chronic forms of pyelonephritis which served as controls.

Results

In most cases of L.C., perivascular and diffuse interstitial fibrosis of the medullae as demonstrated by El-VG staining of kidney sections (Figs. 3 and 4) could be identified very easily with either the naked eye or the aid of a hand lens. Interstitial fibrosis extending into the cortex (Fig. 4) was also easy to see especially when the hand lens was applied for observation. Classification of the histopathologic changes of the kidneys associated with L.C. into three grades (Fig. 1) was therefore easily effected. Such significant fibrosis especially in the perivascular region was not observed even in very advanced chronic pyelonephritis (Fig. 5). Only fibrosis of the medulla parallel to that in the

![Fig. 1. Grading of renal lesions associated with cirrhosis of the liver.](image-url)
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Fig. 2. Grade 0. Renal lesion associated with L.C., showing only very slight perivascular fibrosis (arrows). El-VG stain. X10.

Fig. 3. Grade 1. Perivascular fibrosis (arrows) and diffuse interstitial fibrosis in the medulla (lower half of the photomicrograph). El-VG stain. X10.

Fig. 4. Grade 2. Interstitial fibrosis in the cortex (upper half of the photomicrograph) in addition to the findings of Fig. 3. El-VG stain. X10.

Fig. 5. A pyelonephritic kidney as a control for Figs. 2 to 4, showing diffuse interstitial fibrosis, not especially significant in the perivascular regions (arrows), unlike in L.C. El-VG stain. X10.
Fig. 6. Higher magnification of the portion with the arrow on the right side of Fig. 4. Perivascular fibrosis (arrow in the lower left corner: arcuate vein) extends towards the cortex (arrow in the upper portion). El-VG stain. ×100.

Fig. 7. Higher magnification of Fig. 4, showing perivenous fibrosis causing atrophy of the venous muscular complex (M). The arrow indicates perivenous lymphocytic infiltration. El-VG stain. ×200.

Fig. 8. A glomerulus showing extensive dilatation of the vascular pole and capillaries. PAS stain. ×400.

Fig. 9. A pyelonephritic kidney showing diffuse cellular infiltration (arrows) in the interstitium and hypertrophy of the venous muscular complex (M). El-VG stain. ×100.
milder group among grade 1 renal lesions in L.C. was seen in some cases of chronic pyelonephritis (Fig. 5). On higher magnification of tissue sections under a microscope, especially in grade 2, perivascular fibrosis appeared to be even more distinct around the interlobar, arcuate and interlobular veins and often around the arteries nearby, spreading towards the cortex (Fig. 6). The so-called venous muscular complex proposed by Takeuchi [7,8] which occurs around the interlobar, arcuate and occasionally at the beginning of the interlobular veins, seemed to be atrophic through extensive fibrosis but was often more clearly observed encompassed by bright red-stained collagen fibers after El-VG staining of the kidney sections (Fig. 7). The perivascular fibrosis was frequently accompanied by focal lymphocytic infiltration (Fig. 7), although in L.C. unlike in cases of pyelonephritis, the foci of lymphocytic infiltration were localized around blood vessels. In pyelonephritis, the foci of either interstitial fibrosis or cellular infiltration were more widely and randomly distributed and not limited to the vicinity of blood vessels (Figs. 5 and 9). Moreover, extensive perivascular fibrosis like that present in cases of L.C. was not observed in cases of pyelonephritis. Most kidneys in L.C. revealed evidence suggestive of a backward effect of the circulatory disturbances due to the above perivascular fibrosis, such as marked dilatation of the vascular pole of the glomeruli (Fig. 8) and capillaries of the interstitium and veins. Marked dilatation of the vascular poles was not encountered in cases of pyelonephritis. The grades of renal fibrosis and creatinine levels appeared to show some correlation (Fig. 10). The higher grades of renal lesion seemed to have some correlation with type A cirrhosis (Table 1).

Discussion

Glomerular changes in L.C. have been extensively studied by many investigators. In 1959, Bloodworth and Sommers [1] proposed the term “cirrhotic glomerulosclerosis” and suggested a scheme for grading such sclerosis. Subsequently, Salomon et al. [9] and Sakaguchi et al. [10] termed the same changes hepatic glomerulosclerosis instead of cirrhotic glomerulosclerosis. The reason for introducing this change in nomenclature was that the same types of deposits in the capillary wall and the mesangium, thickening of the basement membrane and in-

![Fig. 10. Comparison of creatinine levels and grades of renal lesions associated with cirrhosis of the liver.](image)

<table>
<thead>
<tr>
<th>Creatinine (mg/dl)</th>
<th>Grade</th>
<th>0</th>
<th>1</th>
<th>2</th>
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<tbody>
<tr>
<td>5</td>
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Table 1. Percentage of each grade of renal lesion and the relationship between grades and types of cirrhosis of the liver

<table>
<thead>
<tr>
<th>Cirrhosis of liver</th>
<th>Grade</th>
<th>0 cases</th>
<th>1 cases</th>
<th>2 cases</th>
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<tr>
<td>Nagayo’s types A &amp; B</td>
<td></td>
<td>5 cases (20%)</td>
<td>16 cases (64%)</td>
<td>4 cases (16%)</td>
</tr>
<tr>
<td>(Nagayo’s type A)</td>
<td></td>
<td>0 case (0%)</td>
<td>2 cases (66%)</td>
<td>1 case (33%)</td>
</tr>
<tr>
<td>(Nagayo’s type B)</td>
<td></td>
<td>5 cases (23%)</td>
<td>14 cases (63%)</td>
<td>3 cases (13%)</td>
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</table>
creased mesangial matrix were observed electron-microscopically in other chronic hepatic disorders besides L.C. In addition, Fisher and Hellstrom [11] and Fisher and Perez-Stable [12] presumed such hepatic glomerulosclerosis to comprise membranous proliferative and lobular glomerulonephritis. Callard et al. [13] confirmed the same changes as immune complex type glomerulonephritis with the aid of immunofluorescent microscopy. Berger et al. [14] reported that deposits with IgA as a component were frequently present in the glomeruli of patients with L.C. Most of these investigators therefore considered that renal changes related to hepatic disorders are localized in the glomeruli as a form of glomerulonephritis. In the present study, glomerular changes as proposed by Bloodworth and Sommers [1] were also observed in almost half of the cases. However, the author did not examine the glomerular lesions further since the main aim of the study was to elucidate the causes of the circulatory disturbance. Concerning changes other than glomerular ones which could possibly cause circulatory disturbance, no report has yet been published insofar as the author is aware. Such a paucity of research might suggest a lack of remarkable changes to attract the attention of pathologists. Nevertheless, from the clinical standpoint, Epstein et al. [2] did describe the presence of circulatory disturbances in L.C. based on an angiographic study of kidneys before and after the death of a patient with L.C., as mentioned earlier. The present author's results demonstrating interstitial fibrosis which was especially significant in the perivascular region, occasionally accompanied by focal lymphocytic infiltration, may support the disturbance of the renal circulation indicated by Epstein et al. [2].

Such perivascular fibrosis appeared to involve especially the so-called venous muscular complex proposed by Takeuchi [7, 8], since in L.C. this portion was also stained more vividly red by El-VG stain than any portion of the interstitium in pyelonephritis. Concerning the characteristics of this complex, much has yet to be determined. However, the vascular abnormality reported by Epstein et al. [2] seems to be best explained if this venous muscular complex has the ability to squeeze out the venous blood of the kidney towards the vena cava, so introducing fresh blood flow from the renal artery. The complex might also regulate the flow in the arteries during such squeezing out since it also encompasses the arteries as well as the veins. Damage to this complex associated with interstitial fibrosis would therefore cause significant impairment of the renal circulation even if the damaged areas were small and so neglected by most histopathologists. In this respect, the present results also cast some light on the mechanisms of the renal circulation. The presence of fibrosis leading to disturbance of renal function was also suggested by the clinical data, as shown in Fig. 10, in which some correlation appeared to exist between the proposed renal lesions and higher creatinine levels. This might be consistent with the findings of Bohle et al. [15-17] who reported a relationship between interstitial fibrosis and elevation of the creatinine levels in patients. The grades of renal and hepatic lesions may also be correlated, since the rate of type A cirrhosis appeared to some extent to correspond with the grades of the renal lesions. However, it is too early to draw any firm conclusions in view of the fact that the author's present cases were limited in number.

As regards the chronological relationship between the perivascular and interstitial lesions, some suggestions can be drawn from the work of Burck and Gayer [18] who reported that diffuse interstitial fibrosis is a remnant of long-lasting acute renal failure, developing out of interstitial edema. Thus, the primary cause of edema in cases of L.C. must be more central in the vascular system. In this light, it seems reasonable to consider that perivascular fibrosis occasionally with lymphocytic infiltration around the interlobular and arcuate veins would appear first as a cause of interstitial edema of the rest of the renal interstitium. So far, however, no report has given details of such interstitial edema, fibrosis or cell infiltration in the kidneys in hepatopathy. The author believes that interstitial changes of the kidney in L.C. should be reexamined systematically.

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References