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Original Article

Clinical usefulness of kidney biopsy in liver transplant recipients with renal impairment

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Abstract

Background: Chronic kidney disease is a common complication after liver transplantation. In this study, we analyzed the results of kidney biopsy in liver transplantation recipients with renal impairment.

Methods: Between 1999 and 2012, 544 liver transplants were performed at our hospital. We retrospectively analyzed the clinical and histological data of 10 liver transplantation recipients referred for kidney biopsy.

Results: The biopsies were performed at a median of 24.5 months (range, 3–73 months) after liver transplantation. The serum creatinine level was 1.81 ± 0.5 mg/dL at the time of kidney biopsy. There were no immediate complications. The most common diagnosis was glomerulonephritis (GN), such as immunoglobulin A nephropathy ($n=4$), mesangial proliferative GN ($n=1$), focal proliferative GN ($n=1$), and membranous GN ($n=1$). Typical calcineurin inhibitor (CNI)-induced nephrotoxicity was detected in three cases (30%). Chronic tissue changes such as glomerulosclerosis, interstitial fibrosis, and tubular atrophy were present in 90%, 80%, and 80% of cases, respectively, and mesangial proliferation was detected in 40% of cases. We began treatment for renal impairment based on the result of kidney biopsy; for example, angiotensin-receptor blockers or steroids were prescribed for GN, and the CNI dose was reduced for CNI nephrotoxicity. As a result, eight of 10 patients showed improvement in glomerular filtration rate, but two progressed to end-stage renal disease.

Conclusion: Kidney biopsy is a safe and effective method for determining the cause of renal impairment after liver transplantation. Management of patients based on the result of kidney biopsy may improve renal outcomes.

Introduction

Renal impairment is a commonly detected problem after liver transplantation (LT), and the cumulative incidence of chronic kidney disease (CKD) in liver transplant recipients is estimated at 18.1% at 5 years [1]. Proper management of renal

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impairment is possible only after the underlying etiology of the renal injury has been clearly identified. In this regard, kidney biopsy is a very important instrument for determining the cause of renal impairment and deciding on the appropriate management plan in liver transplant recipients.

However, until now, only a few reports have used kidney biopsies to investigate the cause of renal impairment, and these studies have had contradictory results. For example, some reports have suggested that calcineurin inhibitor (CNI)-induced nephrotoxicity is the main cause of renal impairment [2–5]. By contrast, other recent reports proposed that kidney pathology after LT is variable and not limited to CNI toxicity [6–8]. In addition, the main cause of hepatic failure in Korea is hepatitis B, which is significantly different from that in the Western population where hepatitis C plays the main role [5,9–11]. Considering that the cause of the chronic liver disease may affect the pathology of renal disease, the renal histology in liver transplant recipients with renal impairment in Korea may have a different pattern than that in the Western population, as reported previously [7,8,12].

For these reasons, we analyzed the results of kidney biopsies in liver transplant recipients with renal impairment and investigated whether kidney biopsy is useful for guiding the management of renal impairment.

Methods

Patient group

Between 1999 and 2012, 544 liver transplants were performed at our center. In this study, we included 10 patients who underwent kidney biopsy because of unexplained increase of serum creatinine ($n=6$), newly developed proteinuria [>1 g protein/g creatinine (g/g) in random spot urine; $n=2$], and proteinuria (>0.5 g/g) accompanied with microscopic hematuria ($n=2$). Clinical and histological data were extracted from the patients' electronic medical records. We reviewed several variables, including each patient's demographic data, laboratory findings, medication history, and the findings of the kidney biopsy. Renal function was assessed by calculating the estimated glomerular filtration rate (eGFR) using the modification of diet in renal disease equation [13]. The amount of proteinuria was quantified with a 24-hour urine collection at the time of biopsy. This study was approved by the Institutional Review Board of our institution (KC13RISI0327).

Biopsy procedure

All patients underwent standard percutaneous biopsies performed by experienced nephrologists under ultrasound guidance, using an automatic spring-loaded core biopsy system. Biopsy specimens were collected for light microscopy (hematoxylin–eosin, periodic acid–Schiff, silver methenamine, and trichrome staining), immunofluorescence, and electron microscopy. All biopsies were reviewed by a single experienced renal pathologist at our institution. Morphologic entities were defined by standard criteria.

Statistical analysis

Continuous variables are presented as median and interquartile range or mean $\pm$ standard deviation. The results were considered significant when $P<0.05$. Statistical analysis was performed using the SPSS version 11.5 (SPSS Inc., Chicago, IL, USA).

Results

Baseline characteristics of the patient population

The baseline characteristics of the study participants are summarized in Table 1. The most common primary liver disease was hepatitis B ($n=8$); there was one case each of alcoholic liver cirrhosis and portal vein thrombosis. In three patients, hepatocellular carcinoma was combined prior to LT. In all patients, liver function was stable, according to the results of liver function tests, platelet counts, prothrombin international normalized ratio, and albumin level. The main immunosuppressive drug used was tacrolimus in eight patients, and cyclosporine (CsA) was used in two patients. In nine patients, diabetes mellitus was combined, and in two of these patients, diabetes mellitus developed after LT.

Renal manifestations in the patient population

Kidney biopsy was performed at 24.5 months (3–66 months) after LT, and the mean age at biopsy was 50.3 ± 8.2 years. The indications for biopsy were elevated serum creatinine (Scr) level in six cases, proteinuria in two cases, and proteinuria with hematuria in two cases. At the time of biopsy, Scr level was 1.8 ± 0.5 mg/dL, and eGFR was 42.2 ± 13.9 mL/min/1.73 m^2. The 24-hour urine protein excretion was 6.3 ± 10.1 g/day, and nephrotic-range proteinuria was found in three patients. Drug concentrations (trough level) were 5.3 ± 1.5 ng/mL in the eight patients using tacrolimus and 189.4 ± 64.5 ng/mL in the two patients using cyclosporine (Table 1). After kidney biopsy, there were no immediate complications.

Histologic findings of kidney biopsy

Histopathological findings are summarized in Table 2. All biopsy specimens were adequate for diagnosis, and the number

Table 1. Patients characteristics at the time of kidney biopsy

	Value
Gender (male)	10 (100)
Mean age at Kidney biopsy	50.3 ± 8.2
Duration between LT and Kidney Bx (mo)	24.5 ± 25.4
Origin of liver disease	
HBV	8 (80)
HCV	0 (0)
Alcoholic liver cirrhosis	1 (10)
portal vein thrombosis	1 (10)
Diabetes mellitus	7 (70)
Hypertension	2 (20)
HCC	3 (30)
AST(U/L)	32.4 ± 21.7
ALT(U/L)	54.1 ± 58
Platelet (10^9/L)	192.1 ± 109
INR	1.05 ± 0.13
Immunosuppresive treatment	
Tacrolimus	8 (80)
Cyclosporine	2 (20)
Tacrolimus level(ng/mL)	5.31 ± 1.5
Cyclosporine level(ng/mL)	189.4 ± 64.5
Serum Creatinine(mg/dL)	1.8 ± 0.5
eGFR by MDRD(mL/min/1.73m^2)	42.2 ± 13.9
24hr urine protein(g/day)	6.3 ± 10.1
Proteinuria > 3g/day	3 (30)
Proteinuria < 3g/day	7 (70)

Data are presented as mean ± SD or n (%).

Table 2. Histopathologic findings

Case	Light microscopy*										Immunofluorescence
	GGS/GI	MM	GBMt	GNE	Int.F	TA	AS	AH	ATN	SpLe	
1	1/4	++	N	N	++	++	N	N	N	IgA, CIN	IgA, IgM, C3
2	1/11	N	N	N	++	++	+	N	N	CPN	IgG, IgA, IgM, C3, κ, λ
3	2/18	++++	N	N	++	++	N	N	N	IgA	IgA, IgG, IgM, C3, κ, λ
4	0/14	+	N	N	++	++	++	N	N	IgA, Arteriosclerosis	IgA, IgM, C4d, C1q, κ, λ
5	0/7	N	N	N	N	N	N	N	N	CIN	IgG, IgA, C4d
6	0/8	+++	N	N	N	N	+++	N	N	MsPGN	N/A
7	1/5	++	N	N	++	++	+	+++	N	FPGN, CIN	IgG, IgA, IgM, C3, κ, λ
8	1/12	+	+++	N	+	+	N	N	N	MGN	IgA, Ig, C1q
9	5/8	++	N	N	+++	+++	+	+++	N	Arteriosclerosis, DN	IgG, IgM
10	16/28	++	N	N	+++	+++	++	N	N	IgA	IgA, IgM,C3, κ, λ

* Affected degree: N, nonspecific finding; +, <20%; ++, 20–40%; +++, 40–70%; ++++, > 70%.
AH, arterial hyalinosis; AS, arteriosclerosis; ATN, acute tubular necrosis; CIN, calcineurin inhibitor nephrotoxicity; CPN, chronic pyelonephritis; DN, diabetic nephropathy; FPGN, focal proliferative glomerulonephritis; GBMt, glomerular basement membrane thickening; GGS, global glomerulosclerosis; GI, glomeruli; GNE, glomerularnodular expansion; Int.F, interstitial fibrosis; IgA, immunoglobulin A nephropathy; MGN, membranous glomerulonephritis; MM, mesangial matrix proliferation; MsPGN, mesangial proliferative glomerulonephritis; N/A, not applicable; SpLe, specific histological lesions; TA, tubular atrophy.

Table 3. Clinical outcomes after kidney biopsy

Case	Age/ Gender	Cause of LD	HTN	DM	Indication of KB	Time from LT to KB (mo)	SCr at KB	Immuno-suppresion at KB	Pathologic diagnosis	SCr at last f/u	Renal replacement therapy
1	32/M	CHB	−	−	SCr ↑	4	2.08	TK	IgA, CIN	1.49	–
2	61/M	PVT	−	+	SCr ↑	12	2.75	TK+MMF	CPN	1.2	–
3	45/M	CHB	−	−	SCr ↑	21	1.67	TK	IgA	1.05	–
4	54/M	CHB	−	+	Prot/H	13	1.84	CsA	IgA, arteriosclerosis	1.45	–
5	46/M	CHB	−	+	SCr ↑	73	1.8	TK+MMF+ST	CIN	1	–
6	49/M	CHB	−	−	Prot/H	4	1.05	TK+MMF+ST	MsPGN	0.88	–
7	56/M	CHB	+	+	SCr ↑	16	2.27	TK+MMF+ST	FPGN,CIN	7.9	+ (HD)
8	49/M	CHB	−	+	Prot	3	1.09	CsA	MGN	1.19	–
9	40/M	CHB	+	+	Prot	66	1.7	CsA+ST	DN, arteriosclerosis	11.42	+ (PD)
10	51/M	ALC	−	+	SCr ↑	33	1.8	TK	IgA	2.15	–

ALC, alcoholic liver cirrhosis; CHB, chronic hepatitis B; CsA, cyclosporine; CIN, calcineurin inhibitor nephrotoxicity; CPN, chronic pyelonephritis; DM, diabetes mellitus; DN, diabetic nephropathy; FPGN, focal proliferative glomerulonephritis; H, hematuria; HD, hemodialysis; HTN, hypertension; IgA, immunoglobulin A nephropathy; KB, kidney biopsy; LD, liver disease; LT, liver transplantation; MGN, membranous glomerulonephritis; MMF, mycophenolic acid; MsPGN, mesangial proliferative glomerulonephritis; PD, peritoneal dialysis; PVT, portal vein thrombosis; Prot, proteinuria; SCr ↑, serum creatinine elevation; ST, steroid; TK, tacrolimus.

of observed glomeruli was 11 ± 7 on light microscopy study. In most patients, chronic change was detected; the findings included glomerulosclerosis in 90% (9/10), global glomerulosclerosis in 70% (7/10), interstitial fibrosis in 80% (8/10), tubular atrophy in 80% (8/10), and vascular fibrous wall thickening in 60% (6/10). Additionally, mesangial cell proliferation was found in 40% (4/10). In seven out of 10 patients, GN was diagnosed; immunoglobulin A nephropathy (IgAN) was the most common diagnosis ($n=4$), followed by mesangial proliferative GN ($n=1$), focal proliferative GN (FPGN; $n=1$), and membranous GN (MGN; $n=1$). In the remaining two cases, there was chronic pyelonephritis (PN) and diabetic nephropathy, respectively. Out of the 10 patients, typical CNI nephrotoxicity was observed in three. Electron microscopy was performed in three patients who were diagnosed with IgAN ($n=2$) and chronic PN ($n=1$). In the two patients with IgAN, podocyte foot process effacement was observed, and in the patient with chronic PN, immune complex deposits were seen in the mesangial basement membranes.

Clinical outcome after kidney biopsy

Table 3 depicts the clinical outcome after kidney biopsy during the follow-up period of 47.1 months (range, 6–112 months). Based on the result of kidney biopsy, we began specific therapy for each patient. In the four patients who were diagnosed with IgAN, we started angiotensin-receptor blockers. In the two patients with nephrotic proteinuria, who were ultimately diagnosed with FPGN or MGN, we used steroid therapy with prednisolone (1 mg/kg). In the patient with chronic PN, we initiated antibiotic therapy. In the three patients with CNI nephrotoxicity, we reduced the dose of calcineurin inhibitor by 20%. After treatment, Scr level showed improvement in eight cases (1.76 ± 0.54 mg/dL at biopsy vs. 1.36 ± 0.54 mg/dL at last follow-up; $P=0.062$). However, renal impairment did not improve and progressed to end-stage renal disease in two cases after 6 months and 35 months each. These patients (Cases 7 and 9) required hemodialysis and peritoneal dialysis.

Discussion

In liver transplant recipients, many risk factors, such as the progression of underlying renal disease, hemodynamic factors during the operation, metabolic problems, and nephrotoxic agents, can lead to the deterioration of renal function [14,15]. Proper management of renal impairment in liver transplant recipients is important because the development of CKD in liver transplant recipients is a major risk factor for patient mortality [16]. In this study, we analyzed the various histopathological diagnoses from kidney biopsies performed in liver transplant recipients, and we found that kidney biopsy is useful for determining the possible etiology of the renal impairment and, even more, for suggesting a specific management plan for liver transplant recipients.

The most characteristic finding in the renal histology of this study population was chronic renal tissue injury rather than acute inflammation. Global glomerulosclerosis was found in 70% (7/10) of biopsies, and the sclerosis percentage of the total glomeruli was $19.3 \pm 30.0\%$. Tubulointerstitial fibrosis worse than Grade 2 was detected in 70% of biopsies. In patients with advanced liver disease, a significant portion of them showed advanced CKD as shown previously [17]. In addition, CNI may aggravate the progression of CKD. Hence, we thought that both pre-existing renal lesion and post-transplant change are associated with the chronic kidney lesion in those patients.

By contrast, acute lesions, such as mesangial proliferation and interstitial infiltration, are relatively less common. The Scr level at biopsy was only 1.8 ± 0.5 mg/L, and 18% of patients had a normal Scr level at the time of biopsy, which suggests that even though a decrease in renal function might not be apparent, histologic findings may show advanced tissue injury in liver transplant recipients.

The most common histologic diagnosis in this study was GN ($n=7$) and six GN patients were infected with hepatitis B virus (HBV). It is well known that some types of GN, especially membranous GN, show significant association with HBV infection [18]. However, three of six cases of GN infected with HBV were IgAN, whose association with HBV infection has not been established in previous reports [19,20]. Thus, the large number of IgAN cases in this study may accidently result from a high prevalence of IgAN in Korean society [21]. Another possible reason is that patients with underlying IgAN may be more vulnerable to kidney injury after liver transplantation. However, this issue could not be clarified due to the limited case number of this study.

The prevalence of CNI nephrotoxicity was lower in this study than in previous reports [5,22,23]. Indeed, typical CNI nephrotoxicity was found in 30% of cases (3/10), and it appeared to be the main cause of renal impairment in only one case. However, this result does not underestimate the importance of CNI nephrotoxicity, which has been emphasized in many previous reports [5,22,23]. The possible reason for the lower incidence of CNI nephrotoxicity is that the time from the LT to the kidney biopsy was relatively short, and, even more, the CNI level had been kept low in most patients. Thus, another renal disease may have caused the renal impairment prior to when typical chronic CNI nephrotoxicity developed.

We decided on the appropriate management plan based on the histologic diagnosis; for example, angiotensin-receptor blockers were prescribed for IgAN, steroid pulse therapy for MGN or mesangial proliferative GN, antibiotics for chronic PN, and dose reduction was used in patients with CNI nephrotoxicity. After the initiation of treatment, improvement of renal function occurred in eight out of 10 patients. In patients with CNI nephrotoxicity there was marked improvement; a significant decrease in the Scr level was found within several weeks of the reduction in the CNI dose. These findings suggest that, in many cases, specific therapy based on the results of kidney biopsy can delay or reverse the progression of CKD.

Meanwhile, two patients did not respond to therapy and progressed to end-stage renal disease. One patient had end-stage diabetic nephropathy on kidney biopsy and another patient had FPGN with massive proteinuria, which did not respond to steroid pulse therapy. The common findings of the above patients were advanced chronic injury or massive proteinuria, compared with the other patients with more favorable clinical outcomes. It suggests that early performance of kidney biopsy and aggressive management of liver transplant recipients may be help delay the progression of CKD.

The safety of kidney biopsy is an important issue as well. Even though many liver transplant recipients have the indications for kidney biopsy, only a limited number of cases have been referred for this procedure, possibly because of concerns about bleeding in liver transplant recipients [7]. We checked the laboratory tests associated with excessive bleeding, such as platelet count and activated partial thromboplastin time, and decided to perform the kidney biopsy when the results were within the normal range; as a result, we had no complications secondary to bleeding in this study. Therefore, we suggest that careful examination of the liver function and bleeding tendency is necessary prior to kidney biopsy to avoid serious complication related to it.

The limitation of this study is the small sample size. Only 2% of total liver transplant recipients in our center underwent kidney biopsy for the evaluation of renal impairment. Considering that about two-thirds of liver transplant recipients suffer chronic kidney injury, an analysis performed on a larger study population may be warranted.

Nevertheless, this study showed that kidney biopsy is safe and useful for diagnosing various patterns of renal disease that are not limited to CNI nephrotoxicity. Moreover, our results suggest that a kidney biopsy may help to determine the specific management plans required to improve renal impairment in liver transplant recipients.

Conflict of interest

The authors declare no conflicts of interest.

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