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CASE REPORT

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Steroid therapy is effective for IgA nephropathy after liver transplantation in a pediatric patient

Hiroshi Tamura | **Shohei Kuraoka** | **Hitoshi Nakazato**

Faculty of Life Sciences, Department of Pediatrics, Kumamoto University, Kumamoto, Japan

Correspondence
Hiroshi Tamura, Faculty of Life Sciences, Department of Pediatrics, Kumamoto University, 1-1-1 Honjo, Chuo-ku, Kumamoto 860-8556, Japan.
Email: bohm1905HT@kuh.kumamoto-u.ac.jp

Abstract

Hepatic IgA nephropathy is a complication of chronic liver disease. IgA nephropathy after liver transplantation is rare, especially in children, and carries a significant risk factor for chronic renal failure and mortality. In cases without viral hepatitis, steroid therapy may be useful for IgA nephropathy associated with liver dysfunction.

KEYWORDS

child, IgA nephropathy, liver transplantation, steroid therapy

1 | INTRODUCTION

IgA nephropathy is the most common cause of primary glomerulonephritis in the most developed countries of the world.[1] The mechanism of IgA nephropathy onset remains incompletely understood. Hepatic IgA nephropathy is a complication of chronic liver disease in adults, especially alcoholic or other cirrhosis and chronic hepatitis.[2,3] In particular, it is rare in children, and few reports on pediatric IgA nephropathy after liver transplantation (LT) have been reported.[4,5] We report the case of a 12-year-old girl who developed IgA nephropathy after liver transplantation (LT).

2 | CASE PRESENTATION

The patient was a 12-year-old girl. At the age of 5 years, she developed liver failure because of primary sclerosing cholangitis (PSC), and LT was performed with her father as the donor. When she was 7 years old, hepatobiliary enzyme elevation was observed, and endoscopic retrograde cholangiopancreatography (ERCP) was performed, and PSC recurrence was diagnosed. Although she had been registered for brain-dead liver transplantation, she underwent living-donor LT with her mother as the donor due to exacerbation of liver dysfunction and hyperbilirubinemia triggered by infection. She did not have proteinuria, hematuria, and renal dysfunction at the time of second LT. The patient was treated with tacrolimus (TAC) and prednisolone (PSL) for preventing rejection. At 9 years of age, urinary occult blood was detected in school urinalysis. At 12 years of age, asymptomatic proteinuria, as well as microscopic hematuria, were detected in the school urinalysis, and she visited our hospital. Her weight was 42 kg (–0.3 SD), height was 141 cm (–1.9 SD), and blood pressure was 102/60 mm Hg. Her serum creatinine level was 0.48 mg/dL and urinary protein creatinine ratio was 2.0 g/mgCr. Red blood cells (>100) per high-power field were observed. The patient's erythrocyte sedimentation rate, C-reactive protein level, and complete blood count were normal. Aspartate transaminase (17 U/L), alanine transaminase (10 U/L), gamma-glutamyl transpeptidase (27 U/L), alkaline phosphatase (658 U/mL), and lactate dehydrogenase (183 U/L), were normal. Total bile acid increased slightly to 10.6 μmol/L. Antinuclear antibodies, antiglomerular basement membrane antibody, perinuclear antineutrophil cytoplasmic antibody, and cytoplasmic antineutrophil cytoplasmic antibody, were normal. No viral infections, such as hepatic B virus infection and hepatic C virus, were present. Computed tomography revealed the splenorenal shunt (Figure 1). A renal biopsy was performed for differential diagnosis of chronic nephritis syndrome and calcineurin inhibitor-associated nephropathy. Light microscopy revealed that the mesangial matrix increased in a segmental manner

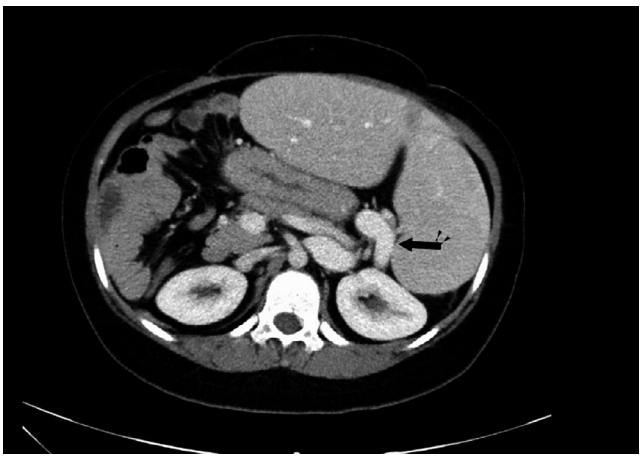

FIGURE 1 Computed tomography revealed the splenic kidney shunt, as indicated by arrows

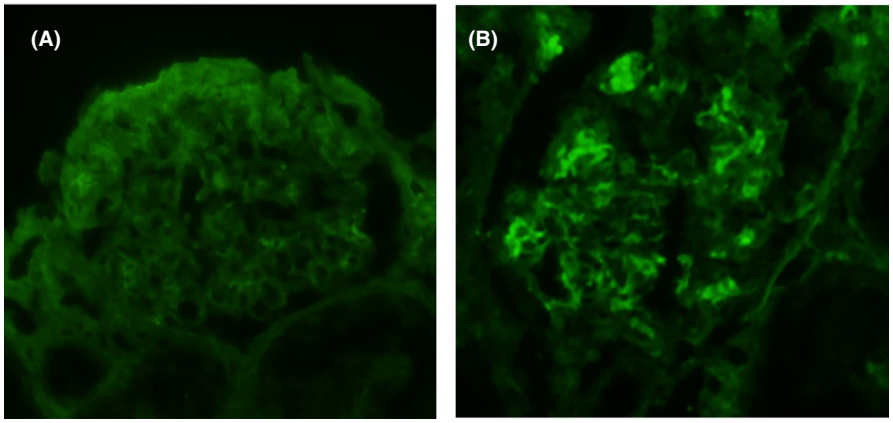

FIGURE 2 A, IgA1 staining (immunofluorescence, original magnification ×400). B, IgA2 staining (immunofluorescence, original magnification ×400). Immunofluorescent microscopy revealed mesangial deposits of IgA2 predominantly

in the glomeruli. Adhesion of Bowman's sac was observed in some glomeruli, and cellular crescent was observed in one of 9 glomeruli. Tubular injury due to calcineurin inhibitor was not observed. Immunofluorescent microscopy revealed mesangial deposits of IgG 1^+, IgA 2^+, and fibrinogen 2^+, and the staining of IgA was predominantly IgA2 (Figure 2). The patient was diagnosed with IgA nephropathy. The PSL dose was increased from 5 mg/d to 65 mg/d (2 mg/kg/d), and TAC was continued at the same dosage of 2.4 mg, and angiotensin-converting enzyme was used to follow the Clinical guideline for Japanese pediatric IgA nephropathy. The PSL dose was reduced to 20 mg because of cytomegalovirus (CMV) infection, 3 weeks thereafter that was successfully treated with ganciclovir. IgA nephropathy gradually improved, resulting in complete remission after 3 months. No recurrence has occurred even after 3 years of onset.

3 | DISCUSSION

Hepatic IgA nephropathy is considered a type of secondary IgA nephropathy and frequently occurs with liver disease, especially alcoholic liver disease.[3] The mechanism of development of hepatic IgA nephropathy is believed to be as follows: The hepatic clearance of IgA and IgA-type immune complexes in the blood is reduced because of a decrease in Kupffer cell function, and the IgA-type immune complexes are deposited on the renal glomerular mesangium.[3,6] IgA produced by plasma cells in the lamina propria of the intestinal mucosa, except for those secreted into the lumen of the intestinal tract reaches the liver via portal venous blood, and is excreted in the bile via hepatocellular membrane receptors. It is assumed that hepatic circulation is impaired and that the presence of a portal venous shunt causes IgA-type immune complexes to deposit on the glomeruli without being processed by the liver.[7] In alcoholic liver disease, IgA-containing cells in the lamina propria of the intestinal mucosa increase, and the IgA production increases. It is thought that the increased IgA production and metabolic disorders in these chronic liver disorders are involved in the development of hepatic IgA nephropathy.[7]

Majority of primary IgA nephropathy cases are based on IgA1 deposition at the glomeruli, while hepatic IgA nephropathy due to alcoholic liver cirrhosis is based on IgA2 deposition.[8] We believe that the presence of the splenorenal shunt and the glomerular staining of IgA2 predominantly caused the IgA2-type immune complex to be deposited on the glomeruli without being processed by the liver owing to the presence of the portosystemic shunt in our case.

The clinical symptoms of hepatic IgA nephropathy are usually mild; however, few studies have reported on hepatic IgA nephropathy, and no cure has been established.[3]

Few trials have assessed IgA nephropathy after LT.[4,5,9,10] In a case report, following the initiation of propranolol and anticoagulant treatment to reduce portal pressure, a gradual decrease in proteinuria and hematuria to normal range was noted.[11] Immunosuppression may also be ineffective in preventing IgA deposition in the kidneys of patients with hepatic IgA nephropathy after LT.[5] In patients who developed IgA nephropathy after LT, it is difficult to select the optimal treatment because they are already being administered immunosuppressive drugs.

TABLE 1 Summary of patients with IgA nephropathy after liver transplantation

Age (years) /sex	Indication of LT	Therapy post LT	Indication of renal biopsy	Duration after LT	Renal pathology	Therapy to nephropathy/ prognosis	Reference
55/M	HBV cirrhosis	sirolimus/MMF	Nephrotic	4 mo	IgA nephropathy	NR/ HD	S1
47/M	HBV cirrhosis	CsA/MMF	Renal impairment	10 y	IgA nephropathy; severe IF/TA; arteriolar hyalinosis	NR/ CKD	S1
56/M	HCV cirrhosis	PSL/MMF	Proteinuria	8 y5 mo	IgA nephropathy; moderate IF/TA; arteriolar hyalinosis	NR/ PTLD died	S1
54/M	HBV cirrhosis	MMF	Acute renal impairment	6 mo	IgA nephropathy; 50% crescent; Mild IF/TA	NR/ died	S1
54/M	HBV cirrhosis	CsA/sirolimus	Renal impairment	1 y1 mo	IgA nephropathy; arteriolar hyalinosis	NR/ died	S2
54/M	HBV cirrhosis	CsA/sirolimus	Renal impairment	1 y3 mo	IgA nephropathy; IF/TA;	NR/ died	S2
62/M	HBV cirrhosis	TAC/ sirolimus	Renal impairment	1 y6 mo	IgA nephropathy; IF/TA; arteriolar hyalinosis; calcineurin inhibitor nephrotoxicity	NR/ NR	S2
57/M	HBV cirrhosis	CsA/sirolimus	Renal impairment	NR	IgA nephropathy; IF/TA; arteriolar hyalinosis	NR/ died	S2
18/F	BA	CsA/AZP/PSL	Renal impairment	17 y	IgA nephropathy; crescents; calcineurin inhibitor nephrotoxicity	NR/ HD	4
3 y6 mo/F	BA	CsA/AZP/PSL	Renal impairment	3 y	IgA nephropathy; crescents, sclerosis; IF/TA	NR/ NR	5
12/F	PSC	TAC/PSL	Proteinuria and hematuria	5 y	IgA nephropathy; 6% crescents, 12% sclerosis	PSL/ CR	This case

Abbreviations: AZP, azathioprine; BA, biliary atresia; CKD, chronic kidney disease; CsA, cyclosporine A; F, female; HBV, hepatitis B virus; HCV, hepatitis C virus; HD, hemodialysis; IF, interstitial fibrosis; LT, liver transplantation; M, male; m, month(s); MMF, mycophenolate mofetil; NR, not reported; PSC, primary sclerosing cholangitis; PSL, prednisolone; PTLD, post-transplant lymphoproliferative disorders; TA, tubular atrophy; TAC, tacrolimus; y, year(s).

Our patient had developed cytomegalovirus infection because of increased steroid levels; however, she eventually achieved remission.

Cases of IgA nephropathy after LT have been investigated previously (Table 1). Total 11 cases, including the present case, have been reported.[4,5,9,10] The patient age ranged from 3 to 62 years, and the subjects included eight male adults and three female children. The cause of liver failure was viral hepatitis in all adult cases, with seven cases of hepatitis B and one case of hepatitis C. In children, there were two cases of biliary atresia and one case of PSC. All the patients had been treated with immunosuppressive drugs to prevent graft rejection after LT. However, to our knowledge, no previous study has reported on the treatment of IgA nephropathy with immunosuppressive drugs. In 9 of the 11 cases prognosis was known; five cases died, two had hemodialysis, one had chronic kidney disease, and one (present case) was in remission of IgA nephropathy. Liver transplant recipients showed that the overall 5-year survival after LT was 74%.[12] Chronic kidney disease may contribute to increased morbidity and early mortality.[13] Therefore, the low survival in the series may be attributed to the presence of kidney disease. Adults may have difficulty with strong immunosuppression because the primary disease is viral hepatitis. The advantage of this case is that kidney disease was detected early during urinalysis performed at the patient's school; therefore, early treatment could be initiated.

4 | CONCLUSION

We reported IgA nephropathy that developed after LT. In this case, the possible direct correlation between IgA nephropathy and portal venous circulation shunt was unclear. IgA

nephropathy after LT is a significant risk factor for chronic renal failure and mortality. We conclude steroid therapy may be useful for IgA nephropathy associated with liver diseases in patients without viral hepatitis.

ACKNOWLEDGMENT

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

SK, HN, and HT: treated the patient. HT and HN performed the analysis. HT wrote the paper.

ETHICAL APPROVAL

All the procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Committee and the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards (64th WMA General Assembly, Fortaleza, Brazil, October 2013). Informed consent for examinations and to publish their cases, including images was obtained from patients and/or their family members.

ORCID

Hiroshi Tamura https://orcid.org/0000-0001-8786-217X

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