Hepatic-Associated Immunoglobulin-A Nephropathy in a Child with Liver Cirrhosis and Portal Hypertension

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ABSTRACT

Hepatic-associated immunoglobulin A (IgA) nephropathy is a relatively common condition that occurs in adults with liver cirrhosis and portal hypertension. However, it is rare in children. This condition is characterized by the deposition of IgA in the renal glomeruli. The present report describes a 14-year-old boy with cryptogenic liver cirrhosis and portal hypertension who presented with hematuria and proteinuria associated with histological changes of IgA nephropathy.

Key Words: Child, cirrhosis, hematuria, IgA nephropathy, portal hypertension, Saudi Arabia

CASE REPORT

A 14-year-old boy was presented with a history of gross hematuria and abdominal distention. The patient also had no history of previous surgical operation, blood transfusion, or use of hepatotoxic or nephrotoxic medications. The parents are not consanguineous, and there was no family history of liver or renal diseases. The physical examination revealed that his vital signs were normal; however, he had pallor, jaundice, hepatosplenomegaly, and ascites.

Laboratory investigations at presentation showed the following: hemoglobin 9 g/dl, platelets $133 \times 10^9$/l, prolonged prothrombin time 16.9 s, prolonged partial thromboplastin time 50.7 s, elevated total bilirubin 37 µmol/l (normal, <17 µmol/l), slightly elevated serum aspartate aminotransferase 51 IU/l (normal, 15–37 IU/l), normal alanine aminotransferase 29 IU/l (normal, 30–65 IU/l), normal alkaline phosphatase 172 IU/l (normal, 100–500 IU/l), normal γ-glutamyl transferase 86 IU/l (normal, 5–85 IU/l), low albumin 31 g/l (34–50 g/l), normal globulin 25 g/l (23–35 g/l), normal IgG level 11 g/l (normal, 5.4–16.1 g/l), normal IgA level 2.45 g/l (0.5–1.9 g/l), elevated blood urea 12.7 mmol/l (normal, 2.3–6.7 mmol/l), and slightly elevated serum creatinine 111 µmol/l (normal, 40–105 µmol/l). Serum C3 and C4 were 1.23 g/l (normal, 0.86–1.84 g/l) and 0.3 g/l (normal, 0.2–0.58 g/l), respectively. The urine examination showed proteinuria (3+), hematuria (red cell count 50 per field), red blood cell casts, and granular casts. The urine protein/creatinine ratio was elevated, 2.37 (normal, <0.03).

Further investigations with the use of upper gastrointestinal endoscopy showed gross esophageal varices, and...
ultrasonography of the abdomen revealed heterogeneous liver with irregular surface with splenomegaly and moderate ascites. Doppler ultrasound examination showed intrahepatic portovenous shunt and varices just posterior to the anterior abdominal wall. The chest X-ray and echocardiography were also normal. The liver biopsy performed after the correction of the deranged coagulation with factor 7 showed grade IV liver cirrhosis but could not reveal the underlying etiology of the disease.

Additional investigations revealed that serum α1-antitrypsin, copper, iron, and ceruloplasmin levels were normal. The urinary copper study was normal, as well as an eye examination for Kayser–Fleischer ring. In contrast, viral hepatitis screen for hepatitis B surface antigen, hepatitis A and C, cytomegalovirus, Epstein-Barr virus, and herpes simplex antibodies were negative. Serum antinuclear antibody, antiliver kidney microsomal antibody, antimitochondrial antibody, perinucleolar antineutrophil cytoplasmic antibody, and serum cryoglobulin were negative. However, serum antismooth muscle antibody was positive at 1:40.

Following the initial evaluation, the patient was discharged and was later readmitted with gross hematuria and hepatic encephalopathy. During the second admission, renal biopsy was performed, which showed mesangial expansion and hypercellularity and glomerular basement membrane thickening [Figure 1]. Immunofluorescence analysis revealed diffuse granular deposits predominantly of IgA (2+), IgM (1+), IgG (1+), and C3c (1+). Examination using electron microscopy showed mesangial and endocapillary proliferation and focal paramesangial dense deposits associated with effacements of the foot processes and focal double contouring of the basement membrane. These features were typical of the IgAN with the membranoproliferative pattern.

**DISCUSSION**

IgAN is commonly reported in adult patients in association with liver cirrhosis and portal hypertension. It has also been reported in adults with chronic hepatitis due to various causes and in noncirrhotic portal hypertension. However, IgAN in children with liver cirrhosis and portal hypertension is rare.

The pathogenesis of hepatic-associated IgAN is not fully understood. The abnormal clearance of the circulating immune complexes by hepatic Kupffer cells may allow them to access the systemic circulation with subsequent deposition in the kidney. Shunting of the portal venous blood to the systemic circulation by passing the liver may increase the renal IgA deposition. Therefore, reduction in the portal pressure is expected to increase the hepatic processing of circulating IgA immune complex. In addition, abnormalities of cellular control of the IgA production that have been described in patients with liver cirrhosis may contribute to the increasing pool of circulating IgA.

Unlike primary IgAN, hepatic-associated IgAN is usually asymptomatic. Although the majority of patients present with microscopic hematuria and proteinuria, others may exhibit gross hematuria. Also some cases may present with mild renal impairment and in rare cases with nephrotic syndrome. In this study, the patient had hematuria and proteinuria with mild renal impairment. Milner et al. reported that hematuria occurred in 66% of the children with end-stage liver disease. The disease usually remains mild and rarely progresses to end-stage renal failure, and there was no correlation found between the severity of liver failure and the extent of the glomerular disease.

Although there was no considerable evidence that improvement in the hepatic disease improves the renal disease, some authors reported an improvement of IgAN with the control of associated portal hypertension. Kalambokis et al. have reported a case of a 34-year-old man with cryptogenic liver cirrhosis and portal hypertension with the resolution of proteinuria and hematuria. The patient had improvement in nephrotic syndrome following hepatic-associated IgAN with the control of portal pressure when treated with propranolol. This study is consistent with that of Nakamura et al., who reported similar findings.

Moreover, in one adult patient with noncirrhotic portal hypertension associated with IgAN, Babbs et al. reported the disappearance of proteinuria and hematuria following splenectomy and resection of a large splenic artery aneurysm.

Figure 1: Section from the kidney biopsy shows two glomeruli, revealing endocapillary proliferation with obliteration of the capillary lumina and lobular accentuation giving a membranoproliferative pattern (hematoxylin and eosin, x200)
The differential diagnoses of concomitant liver and renal disease in children may also include the following: (1) conditions sharing the same etiology, such as congenital hepatic fibrosis and Caroli disease associated with autosomal recessive polycystic kidney disease,\textsuperscript{[13]} (2) chronic viral infection, such as chronic hepatitis B causing membranous nephropathy,\textsuperscript{[14]} or (3) renal impairment in a failing liver due to various causes, occurring as a terminal event, such as hepatorenal syndrome.\textsuperscript{[15]}

In summary, we have demonstrated an additional case of hepatic-associated IgAN that occurs in a child with cryptogenic liver cirrhosis with portal hypertension. Pediatricians dealing with children with chronic liver disease should be aware of such a condition, so that renal-related complications could be anticipated.

REFERENCES

1. Lhotta K. Beyond hepatorenal syndrome: glomerulonephritis in patients with liver disease. Semin Nephrol 2002;22:302-8.
2. Newell GC. Cirrhotic glomerulonephritis: incidence, morphology, clinical features, and pathogenesis. Am J Kidney Dis 1987;9:183-90.
3. Pouria S, Barratt J. Secondary IgA nephropathy. Semin Nephrol 2008;28:27-37.
4. Roccatello D, Picciotto G, Torchio M, Ropolo R, Ferro M, Franceschini R, \textit{et al.} Removal systems of immunoglobulin A and immunoglobulin A containing complexes in IgA nephropathy and cirrhosis patients. The role of asialoglycoprotein receptors. Lab Invest 1993;69:714-23.
5. Giron JA, Alvarez-Mon M, Menendez-Caro JL, Abreu L, Albillos A, Manzano L, \textit{et al.} Increased spontaneous and lymphokine-conditioned IgA and IgG synthesis by B cells from alcoholic cirrhotic patients. Hepatology 1992;16:664-70.
6. Nakamura M, Ohishi A, Watanabe R, Kaneko K, Aosaki N, Iigaya T, \textit{et al.} IgA nephropathy associated with portal hypertension in liver cirrhosis due to non-alcoholic and non-A, non-B, non-C hepatitis. Intern Med 1994;33:488-91.
7. Endo Y, Kanbayashi H. Etiology of IgA nephropathy syndrome. Pathol Int. 1994;44:1-13.
8. Babbs C, Warnes TW, Torrance HB, Ballardie FW. IgA nephropathy in non-cirrhotic portal hypertension. Gut 1991;32:225-6.
9. Milner LS, Houser MT, Kolbeck PC, Antonson DL, McDonald TL, Markin RS, \textit{et al.} Glomerular injury in end-stage liver disease–role of circulating IgG and IgM immune complexes. Pediatr Nephrol 1993;7:6-10.
10. Karashima S, Hattori S, Nakazato H, Awata H, Seguchi S, Ikeda S, \textit{et al.} Membranoproliferative glomerulonephritis in congenital portosystemic shunt without liver cirrhosis. Clin Nephrol 2000;53:206-11.
11. Deviere J, Content J, Denys C, Vandenbussche P, Le Moine O, Schandene L, \textit{et al.} Immunoglobulin A and interleukin 6 form a positive secretory feedback loop: A study of normal subjects and alcoholic cirrhotics. Gastroenterology 1992;103:1296-301.
12. Kalambokis G, Christou L, Stefanou D, Arkoumani E, Tsianos EV. Association of liver cirrhosis related IgA nephropathy with portal hypertension. World J Gastroenterol 2007;13:5783-6.
13. Gunay-Aygun M. Liver and kidney disease in ciliopathies. Am J Med Genet C Semin Med Genet 2009;151C:296-306.
14. Bhimma R, Coovadia HM. Hepatitis B virus-associated nephropathy. Am J Nephrol 2004;24:198-211.
15. Testino G, Ferro C. Hepatorenal syndrome: A review. Hepatogastroenterology 2010;57:1279-84.

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