

Case Report

Remission of membranoproliferative glomerulonephritis associated with a noncirrhotic portosystemic shunt after percutaneous transhepatic portal vein embolization

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Abstract

We present a case of a 75-year-old man with nephrotic syndrome and renal insufficiency caused by immune complex-mediated secondary membranoproliferative glomerulonephritis. He developed hepatic encephalopathy. A congenital portosystemic shunt was identified, indicating a diagnosis of membranoproliferative glomerulonephritis with noncirrhotic portosystemic shunt. Proteinuria resolved after shunt ratio reduction by percutaneous transhepatic portal vein embolization. Renal function and histopathological findings improved without immunosuppressive therapy. This case emphasizes the role of a high shunt ratio and reduced hepatic clearance of circulating immune complexes in such nephropathy. Membranoproliferative glomerulonephritis with a shunt may cause refractory nephrotic syndrome, but embolization is effective.

Keywords: cirrhosis-associated IgA nephropathy; membranoproliferative glomerulonephritis; noncirrhotic portosystemic shunt; percutaneous transhepatic portal vein embolization

Introduction

In patients with a congenital portosystemic shunt, circulating immune complexes (CICs) enter the systemic circulation from the portal blood without hepatic clearance and may be deposited in the glomeruli, leading to nephropathy. This condition is known as membranoproliferative glomerulonephritis (MPGN) with a noncirrhotic portosystemic shunt (NCPSS), and it is a rare disorder for which the optimum treatment remains controversial [1–4]. Because a

high shunt ratio may be important in the onset of MPGN, embolization of the shunt has been proposed [4], but its efficacy remains unclear. We present a patient with nephrotic syndrome, renal insufficiency and a congenital portosystemic shunt.

Case report

A 75-year-old man with peripheral oedema was admitted on 4 November 2005. He had no history of hereditary or genetic disorders, and he did not drink alcohol. Unspecified congenital liver disease and renal dysfunction were noted at a health check in 2004. On admission, physical examination revealed no evidence of inflammation, but he had marked lower limb oedema. Laboratory tests revealed the following: haemoglobin, 120 g/L; leukocytes, 7,000/ μ L; platelets, 12.5×10^4 / μ L; total protein, 43 g/L; albumin, 22 g/L; urea nitrogen, 8.93 mmol/L; creatinine, 124 μ mol/L; serum cholesterol, 10.09 mmol/L; aspartate aminotransferase, 19 IU/L; alanine aminotransferase, 15 IU/L; gamma-glutamyltranspeptidase, 21 IU/L; alkaline phosphatase, 236 IU/L and total bilirubin 20.5 μ mol/L. The C-reactive protein was 0.013 mg/L, while the antinuclear antibody and rheumatoid factor were negative. Serum immunoglobulin G was 6.35 g/L, immunoglobulin A was 3.28 g/L, immunoglobulin M was 1.74 g/L, CH50 was 24.2 U, C3 was 43 U and C4 was 8 U. Tests for hepatitis B virus, hepatitis C virus and cryoglobulins were negative. Urinalysis showed >100 red cells per high-power field and 1–4 leukocytes per high-power field, while the 24-h urinary protein excretion was 8.08 g. Ultrasonography showed an increase of renal cortical echogenicity and a normal liver. A chest radiograph revealed bilateral pleural effusions.

First renal biopsy findings

On 13 December 2005, percutaneous renal biopsy was performed. The specimen contained 19 glomeruli. There were global diffuse endocapillary proliferation, increased

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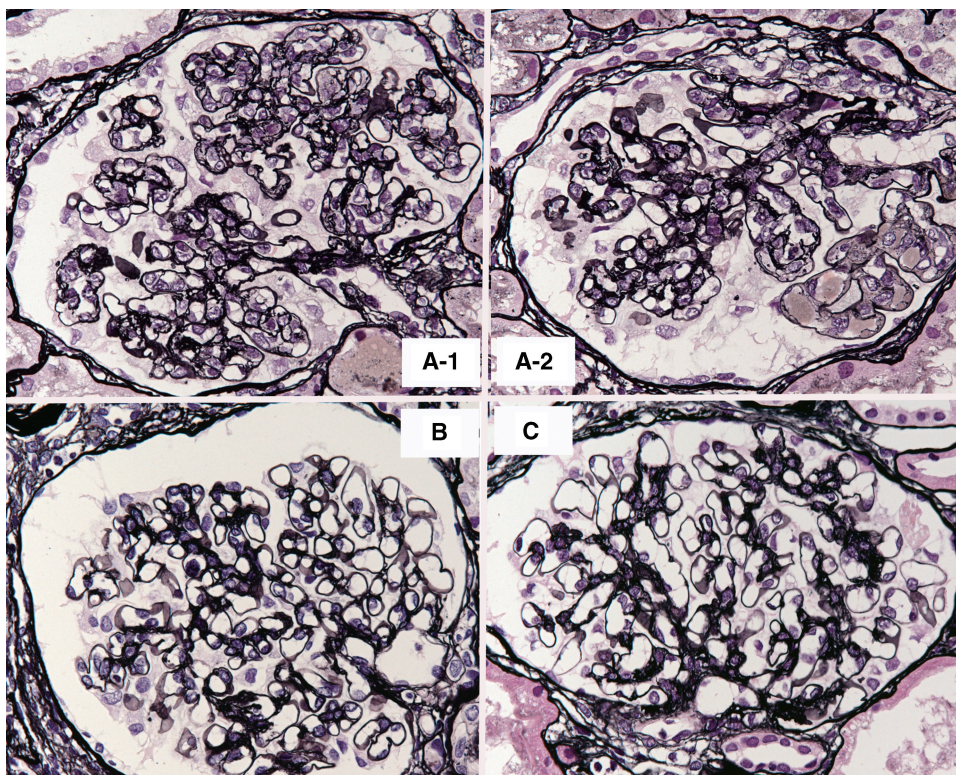


Fig. 1. Light microscopy findings (periodic acid methenamine silver staining: original magnification $\times 400$). (A-1) First renal biopsy: there is diffuse endocapillary proliferation with an increase of mesangial cellularity and matrix, as well as a lobular pattern. The capillary walls are thickened, and the glomerular basement membrane shows a double contour due to the presence of subendothelial deposits and mesangial interposition. (A-2) First renal biopsy: there were also wire loop glomerular lesions, suggesting secondary glomerular disease. The findings show membranoproliferative glomerulonephritis type 1 like. (B) Second renal biopsy: subendothelial deposits and mesangial interposition have decreased. The double contour glomerular basement membrane, lobular appearance and wire loop lesions are no longer detected. The findings resemble mesangial proliferative glomerulonephritis. (C) Third renal biopsy: there are mesangial matrix expansion and an increase of mesangial cellularity. The findings resemble those of IgA nephropathy.

mesangial cellularity and matrix and a lobular appearance. Capillary walls were thickened, and the glomerular basement membrane showed a double contour due to subendothelial deposits and mesangial interposition. There were also wire loop glomeruli, suggesting secondary glomerular disease (Figure 1). Immunofluorescence detected IgA (predominantly), C3, C1q, IgM and IgG with an irregular, chunky capillary and mesangial distribution (Figure 2). Electron microscopy revealed massive subendothelial electron-dense deposits (EDD) and endocapillary proliferation (Figure 3). These results suggested a diagnosis of MPGN type 1 like.

In December 2005, he suddenly lost consciousness. Hepatic function tests and blood glucose were not abnormal, and computed tomography (CT) of the brain was also normal. However, the serum ammonia level was 184 mol/L, so encephalopathy due to hyperammonaemia was diagnosed. Contrast-enhanced CT revealed a large shunt between the left branch of the portal vein and the inferior vena cava. Technetium-99m galactosyl human serum albumin (^{99m}Tc -GSA) scintigraphy showed normal hepatic function. Histological examination of a liver biopsy specimen only revealed mild changes indicating portal hypertension, so he was not affected by cirrhosis. A diagnosis of congenital intrahepatic portosystemic shunt was

confirmed. In March 2006, percutaneous transhepatic portal vein embolization (PTPE) was performed, reducing the shunt ratio to 54.9% of the preoperative level on per rectal technetium-99 m pertechnetate portal scintigraphy. By Day 15 after PTPE, the 24-h urinary protein excretion decreased to 0.25 g. In March 2006, a second renal biopsy was performed. In December 2006, laboratory tests revealed a total protein of 60 g/L, serum albumin of 34 g/L, serum creatinine of 124 $\mu\text{mol/L}$, CH50 of 36.2 U, C3 of 76 U and C4 of 13 U. The urinary protein was negative. Accordingly, his renal function had improved. In December 2006, a third renal biopsy was performed, and ^{99m}Tc -GSA scintigraphy showed minimal deterioration of hepatic function at that time.

Second and third renal biopsies

The specimens contained 20 (March 2000) and 17 (December 2006) glomeruli, respectively. There were mesangial matrix expansion and increased mesangial cellularity. However, endocapillary proliferation, the double-contour glomerular basement membrane and lobular mesangial interposition had all resolved (Figure 1). Immunofluorescence revealed diffuse positivity for IgM, IgA and C3. Staining for IgA was predominantly mesangial.

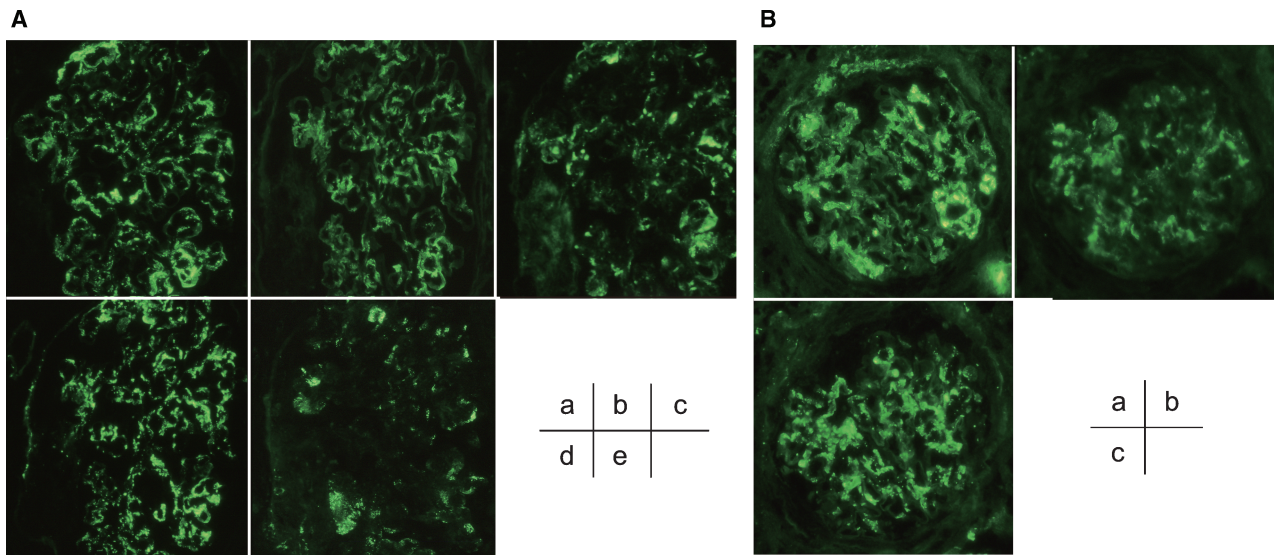


Fig. 2. Findings on immunofluorescence microscopy (all images: original magnification $\times 400$). (A) First renal biopsy: IgA(a) (predominant), IgG(b), IgM(c), C3(d) and C1q(e) show an irregular, chunky capillary and mesangial distribution. This is referred to as 'full house' immunostaining and resembles lupus-associated membranoproliferative glomerulonephritis. (B) Third renal biopsy: there is diffuse positivity for IgA(a), IgM(b) and C3(c). Staining for IgA is predominantly mesangial. C1q and IgG are no longer detected.

C1q and IgG were no longer detected (Figure 2). On electron microscopy, subendothelial deposits and endocapillary proliferation had resolved (Figure 3). The histopathologic findings resembled IgA nephropathy.

Discussion

The present case raises two interesting points. First, in our patient with nephrotic syndrome and secondary immune complex-mediated MPGN who had no predisposing factors (infection, chronic liver disease, hereditary disorders, etc.) except for an NCPSS, shunt embolization achieved remission of nephrotic syndrome and improved renal function without immunosuppressive therapy. Second, renal histopathology changed from an MPGN type 1 like to an IgA nephropathy-like pattern after shunt ratio reduction, while immune complex deposits changed from full house to predominantly IgA and subendothelial EDD disappeared. These changes suggested a causal relationship between NCPSS and this type of nephritis. Moreover, it was demonstrated that CICs cause this disease and that reducing glomerular exposure to immune complexes is beneficial. To our knowledge, this is the first report of such findings.

An NCPSS has a congenital basis that is explained as follows. The embryologic development of the venous system of the trunk involves stages where there are complex collaterals between precursors to the caval system and precursors to the portal veins, persistence of which can lead to anomalous connections [5]. The term 'noncirrhotic portosystemic shunt (NCPSS)' is synonymous with the term 'congenital intrahepatic portosystemic venous shunt (IPSVS)'. Oguz *et al.* found that in most reported cases of congenital IPSVS, the patients were over 50 years old [6–10], although a few paediatric cases have also been reported [3,4]. Congenital

IPSVS is clinically important because it can lead to hepatic encephalopathy. Uchino *et al.* reviewed 51 cases of congenital IPSVS in Japan, and 12 of the patients had hepatic encephalopathy at the time of diagnosis [9]. The natural history of IPSVS depends upon the shunt ratio and on the patient's age, since the frequency of hepatic encephalopathy increases with age. A decrease in the tolerance of the ageing brain to toxic metabolites may explain the late onset of clinical manifestations [7,11]. Large intrahepatic shunts are more often associated with hepatic encephalopathy than small shunts. As the shunt ratio increases, the amount of nitrogen-containing substances from the portal blood that have bypassed hepatic extraction increases in the systemic circulation and this can lead to hepatic encephalopathy. When the shunt ratio exceeds 60%, the risk of hepatic encephalopathy is reported to increase [9,10].

There is much evidence to suggest that MPGN type 1 is a chronic immune complex-mediated glomerulonephritis [12]. Deposition of CICs in the glomeruli is thought to be central to the pathogenesis of MPGN type 1 [13], as well as to the occurrence of secondary MPGN type 1 in patients with known immune complex diseases, such as systemic lupus erythematosus, shunt nephritis, chronic bacteraemia and chronic hepatitis B or C [12]. In addition, acute post-infectious GN and MPGN are frequent in patients with cirrhosis [14,15]. In this patient, all such conditions were negative, so an NCPSS was regarded as a predisposing factor for secondary MPGN type 1. This conclusion was supported by remission of his MPGN and nephrotic syndrome after PTPE. Thus, renal recovery was not spontaneous.

The term 'shunt nephritis' means immune complex-mediated glomerulonephritis that develops as a complication of chronic infection of a ventriculoatrial or (rarely) ventriculoperitoneal shunt inserted for the treatment of hydrocephalus [16]. More than 150 cases have been reported,

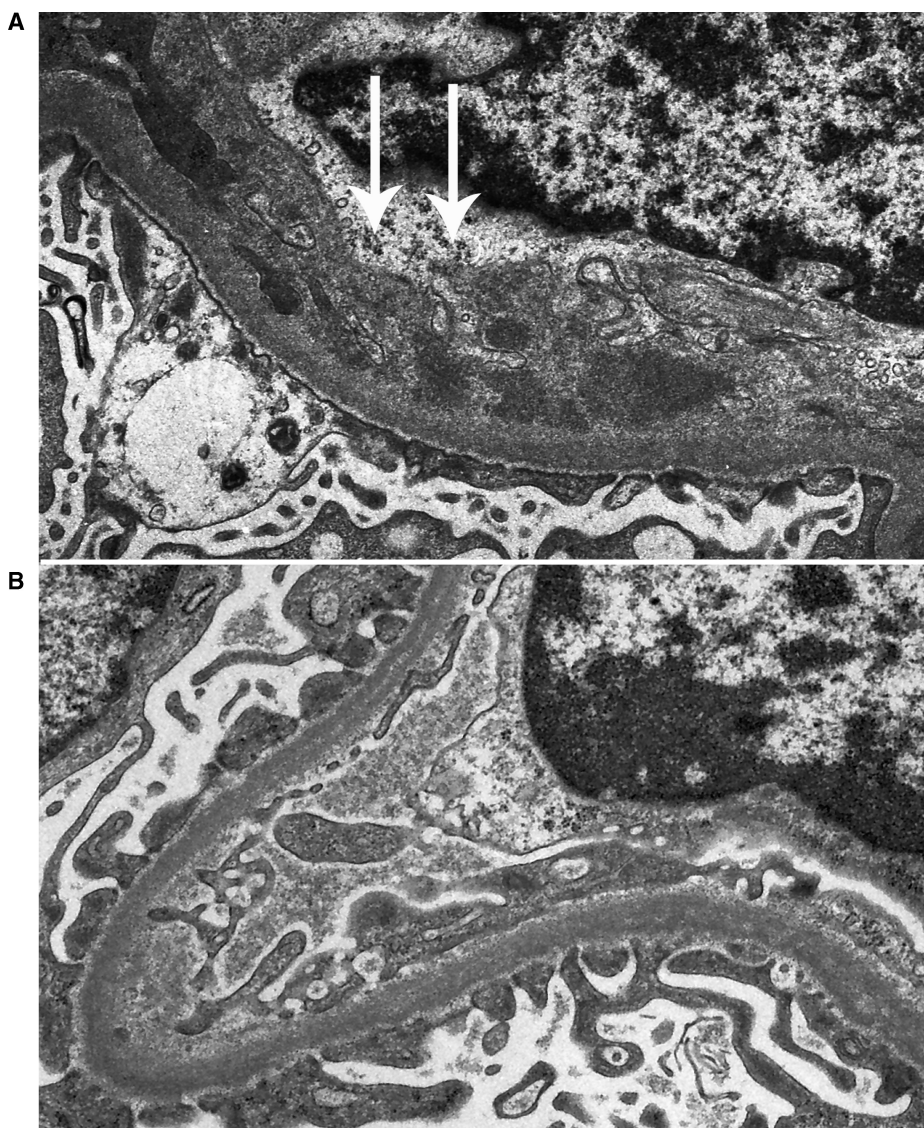


Fig. 3. Findings on electron microscopy (original magnification $\times 6000$). (A) First renal biopsy: massive subendothelial electron-dense deposits (arrow) and endocapillary proliferation suggest a diagnosis of MPGN type 1 like. (B) Third renal biopsy: subendothelial deposits and endocapillary proliferation have resolved.

and the histological findings resemble those of MPGN type 1. Development of shunt nephritis is due to chronic bacteraemia after insertion of a ventriculoatrial shunt. In contrast, our patient did not have shunt nephritis because there was no infection. Also, our patient's renal findings resembled lupus nephritis class IV (World Health Organization). Overexpression of cytokines, chemokines and growth factors induced by the glomerular deposition of CICs is important in the pathogenesis of lupus nephritis [17,18], and CICs were also involved in causing nephritis in our patient. In both shunt nephritis and lupus nephritis, CICs are thought to play a crucial role in the onset of immune complex-mediated glomerulonephritis, so the aetiology of lupus nephritis and our patient's nephritis would seem to be identical or very similar to that of shunt nephritis. The outcome of shunt nephritis is good if early diagnosis and treatment are provided, including intravenous antibiotics and removal

of the infected shunt [19], with the influence of CICs being diminished by treatment of the primary disease. Although there was no infection and our patient had a congenital portosystemic shunt, treatment of the primary disease also decreased exposure of the glomeruli to CICs, which is the same factor that leads to the improvement of shunt nephritis.

Both Soma *et al.* and Karashima *et al.* suggested a causal relationship between NCPSS and the development of nephritis due to reduced hepatic clearance of CICs [3,4]. Karashima *et al.* also speculated that a high shunt ratio ($>90\%$) may trigger such nephritis. Reducing the shunt ratio (54.9%) improved clinical and histological findings in our patient, supporting the hypothesis of Karashima.

Our patient's early renal findings resembled lupus nephritis class IV (World Health Organization). After shunt ratio reduction, the renal histology resembled mesangial proliferative glomerulonephritis with the predominant IgA

deposition. Accordingly, it seems that various immunoglobulins accumulate in the glomeruli when the shunt ratio is high, while IgA from the intestinal tract dominates after the shunt ratio decreases. This case is also suggestive in relation to cirrhosis-associated IgA nephropathy [20]. Although the shunt mechanisms differ, both diseases seem to be caused by reduced hepatic clearance of CICs. The differences of renal pathology probably arise because the type, volume and size of the immune complexes deposited in the glomeruli depend on the shunt ratio.

Since PTPE may decrease liver function, the optimum reduction of the shunt ratio to achieve remission of nephritis and maintain adequate liver function needs to be determined in the future.

In conclusion, the present case revealed that this type of nephritis is reversible at an early stage and that it can be treated by reduction of the shunt ratio. However, it remains difficult to identify a shunt in patients without encephalopathy. When immune complex-mediated nephrotic syndrome is refractory, early screening for NCPSS may be important.

Acknowledgement. The authors thank Yoshifumi Ubara, MD, PhD (Nephrology Center, Toranomon Hospital, 1-3-1, Kajigaya, Takatsu-ku, Kawasaki, Kanagawa, 213-0015, Japan. Tel: +81-44-877-5111; Fax: +81-44-877-5333; E-mail: ubara@toranomon.gr.jp), for his helpful suggestions about this manuscript.

Conflict of interest statement. None declared.

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Received for publication: 16.10.08; Accepted in revised form: 29.1.09