

Hepatitis B virus-associated nephropathy in a patient with diabetes mellitus

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ABSTRACT

Hepatitis B virus (HBV)-associated nephropathy is not a rare manifestation of HBV infection; this could result in diagnostic confusion and the possible misidentification of a diabetic patient with albuminuria. We present the first published case of a HBV-associated nephropathy occurring in a patient with diabetes. The patient was a 24-year-old man who was admitted to hospital with 4 days of generalized swelling and oliguria. He had a 3-year history of weight loss, and a 1-year history of polydipsia and polyuria before the symptoms of generalized swelling and oliguria appeared. Laboratory tests showed a fasting blood sugar of 15.1 mmol/L and glycated hemoglobin of 18.1%. The 24-h urine protein excretion was 2807.8 mg and serum albumin was 19.1 g/L. The diagnosis of HBV-associated nephropathy was confirmed by serological evaluations of HBV antigen and antibodies, immunohistochemical evidence of HBV-related antigens, and immune complexes in renal biopsies. The decreased proteinuria was observed after antiviral therapy.

INTRODUCTION

Diabetes is the leading cause of end-stage renal disease, because diabetic nephropathy develops in 30–40% of patients. However, multiple genetic and environmental predisposing conditions are involved in the development or not of a diabetic nephropathy, therefore supporting the existence of several factors including hepatitis B virus (HBV) infection in the pathogenesis of this disease. Approximately one-third of the world's population has serological evidence of past or present infection with HBV, and 350–400 million people are chronic HBV surface antigen (HBsAg) carriers¹. The prevalence of HBV infection is <1% in the USA, but could be as high as 5–15% in Asia, Africa, the Middle East and eastern Europe². HBV-associated nephropathy is not a rare manifestation of HBV infection; this could result in diagnostic confusion and the possible misidentification of a diabetic patient with macroalbuminuria. We present the first published case of HBV-associated nephropathy occurring in a patient with diabetes. The purpose of the present study was to emphasize HBV-associated nephropathy in the differential diagnosis of clinical proteinuria in patients with diabetes mellitus.

CASE REPORT

The present patient was a 24-year-old man who was admitted to hospital with 4 days of generalized swelling and oliguria. He had a 3-year history of weight loss, and a 1-year history of polydipsia and polyuria before the symptoms of generalized swelling appeared. There was no history of limb anesthesia, impaired vision, papules, oral ulcers or arthralgia. There was a family history of HBV infection. On admission, he was oriented and alert. Blood pressure was 146/108 mmHg. Laboratory tests showed a fasting blood sugar of 15.1 mmol/L, glycated hemoglobin (HbA1c) 18.1% (detected by high performance liquid chromatography using ADAMSTMA1c HA-8160; Arkray, Inc., Kyoto, Japan). With reference to National Glycohemoglobin Standardization Program (NGSP) values by Japan Diabetes Society (JDS)^{3,4}, HbA1c (NGSP;%) is reported to be equivalent to $1.019 \times \text{HbA1c (JDS)\%} + 0.3\%$, which is reasonably estimated by the equation of $\text{HbA1c (JDS)\%} + 0.4\%$. The value of internationally used HbA1c could reach 18.5% in this case, and a fasting C-peptide of 1.03 ng/mL (normal range 1.1–4.0 ng/mL). Glutamate decarboxylase antibody, insulin antibody and insulin cell antibody were all negative. The 24-h urine protein excretion was 2807.8 mg, and serum albumin was 19.1 g/L. Serum cholesterol was 8.06 mmol/L, serum creatinine was 61.9 $\mu\text{mol/L}$ and alanine aminotransferase was 74 U/L. Serum

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aspartate aminotransferase and total bilirubin levels were normal.

Other causes of proteinuria were considered because of the young age onset of diabetes, short duration of diabetes, no evidence of retinopathy, and generalized swelling and oliguria in a short time. HBV-associated nephropathy was suspected after laboratory findings of a normal range of antinuclear antibodies and anti-neutrophil cytoplasmic antibody, with a markedly elevated HBV surface antigen (HBsAg), anti-hepatitis B core antigen and HBV-DNA count (1.15×10^5 IU/mL; normal range, $<1.0 \times 10^3$ IU/mL). Percutaneous renal biopsy was carried out once the patient's general condition had improved. Pathological study showed complete hyalinization of one of 16 glomeruli. The remainder showed a mild increase in the mesangial matrix and mesangial cells, with diffuse thickening of the peripheral capillary walls (Figure 1a). Vascular damage was not observed. There was no evidence of diabetic nephropathy. Immunofluorescence showed diffuse granular deposits of immunoglobulin G (IgG) and C3 in glomerular capillary walls. Electron microscopy showed gross effacement with electron-dense deposits on the subepithelial glomerular basement membrane (Figure 1b). Peroxidase antiperoxidase staining for HBsAg was positive (Figure 1c). Immunofluorescent microscopy showed granular IgG staining along the periphery of the glomerular basement membrane in accordance with HBsAg staining (Figure 1d). The patient was treated with oral entecavir and insulin analogs.

At a follow-up visit 3 weeks later, the HBV-DNA count had decreased to 3.47×10^5 IU/mL, and the 24-h urine protein to 798.6 mg. A total of 8 weeks later, the HBV-DNA count was within the normal range, and the 24-h urine protein was 489.0 mg. The patient was lost to follow-up later.

DISCUSSION

HBV infects more than 300 million people worldwide, with a higher prevalence in developing countries. Chronic HBV infection is associated with an increased risk of end-stage renal disease, which is independent of other potential confounding factors in patients with type 2 diabetes⁵, but to our knowledge, this are no convincing reports of HBV-associated nephropathy in patients with diabetes. A HBV-associated nephropathy has been described in adults, but is more common in children. The diagnosis is based on serological evaluations of HBV antigen and antibodies, immunohistochemical evidence of HBV related antigens, and immune complexes in renal biopsies. In the present case, the diagnosis was further supported by decreased proteinuria after antiviral therapy. Although pathogenesis is unclear, the most widely accepted mechanism is the deposition of immune complexes of viral antigen and host antibody. Membranous glomerulonephritis is the most common form. Liver dysfunction might be mild or absent in many patients. Although most children experience spontaneous remission, approximately 30% of adults progress to renal failure, and up

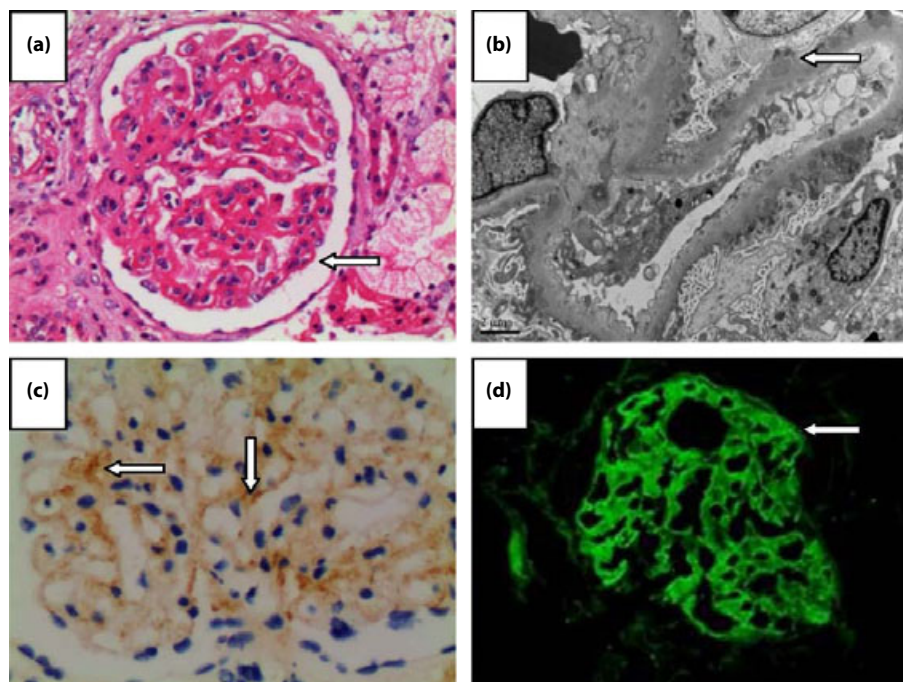


Figure 1 | Renal pathology findings. (a) The glomerulus shows a mild increase in mesangial matrix and mesangial cells, and thickening of the peripheral capillary walls. (b) Electron microscopy shows large electron dense subepithelial deposits in the glomerular basement membrane. (c) Peroxidase antiperoxidase staining for hepatitis B virus surface antigen is positive. (d) Immunofluorescent microscopy shows granular immunoglobulin G staining along the periphery of the glomerular basement membrane.

to 10% require dialysis or a renal transplant. Treatment is primarily antiviral therapy. The most effective method for reducing the incidence of the disease is the use of HBV vaccination⁶.

Nephropathy is a common complication in patients with diabetes. When retinopathy is present, albuminuria can be confidently attributed to diabetic nephropathy⁷. The present case shows the clinical importance of HBV-associated nephropathy and its differentiation from diabetic nephropathy.

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