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Case Report

An unusual renal manifestation of chronic HBV infection

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Abstract

Hepatitis B viral infection is usually a self-limiting disease in immunocompetent individuals. Chronic infection can be seen in up to 5% of infected patients. Renal manifestations of chronic HBV infection are usually glomerular. We describe here an uncommon presentation of a patient with chronic HBV infection with very high viral load and rapidly progressive renal failure. Renal biopsy showed features of tubulointerstitial nephritis and tubular epithelial inclusion bodies suggestive of HBV infection. Entecavir treatment slowed down the progression of his renal disease. Tubulointerstitial nephritis should be considered as a part of the differential diagnosis in patients with HBV infection. Early antiviral treatment may halt the progression of renal disease.

Keywords: Entecavir; HBV infection; interstitial nephritis

Introduction

Hepatitis B virus (HBV) infection usually resolves spontaneously in immunocompetent individuals. However, up to 5% of adult acute hepatitis patients become chronic carriers [1]. The spectrum of chronic HBV infection ranges from asymptomatic infection to chronic hepatitis with progression to cirrhosis, end-stage liver disease and hepatocellular carcinoma [2]. Chronic HBV infection has been associated with various renal manifestations. We describe a rare renal manifestation in a young male with chronic HBV infection.

Case report

A 30-year-old man presented with recent hypertension, severe headache and lethargy on a background of recently diagnosed HBV infection. Blood pressure at presentation was 220/100 mmHg. Neurological examination was unremarkable. Contrast-enhanced computed tomography (CT) scan of the brain was normal. Dipstick urine analysis showed 2+ protein with 1+ blood. There were no dysmorphic red blood cells or casts on microscopy. Urine microalbumin/creatinine ratio was 31.6 mg/mmol of creatinine (<2.5 mg/mmol) with a urine protein excretion of 350 mg/day. Other abnormal investigations included alanine transaminase 108 U/L (5-55), aspartate transaminase 76 U/L (5-55) and erythrocyte sedimentation rate 46 mm/h (0–30 mm/h). HBsAg and Hepatitis B e Antigen (HBeAg) were positive, while IgM Hepatitis B core antibody was negative. Hepatitis B viral DNA was quantitated at 364 million IU/mL. Electrophoresis of serum and urine were negative for paraprotein. He had insignificant cryoprecipitate. Antinuclear antibody, antineutrophil cytoplasmic antibody, extractable nuclear antigen, complements and anti-double-stranded DNA were negative. CT angiogram of aorta and its branches did not reveal any microaneurysm. His blood pressure was well controlled with 10 mg of Perindopril.

Three months after diagnosis, he continued to have high viral load suggesting a chronic HBV infection. Serum creatinine worsened to 134 μmol/L with an estimated glomerular filtration rate (eGFR) of 57 mL/mt. Glomeruli were normal on light microscopy with evidence of tubulointerstitial nephritis (Figure 1A). There was interstitial oedema and dense mononuclear cell infiltrate comprising lymphocytes, plasma cells and occasional eosinophils. Trace deposits of granular IgA (<1+) were seen on immunofluorescence microscopy. Immunohistochemistry also supported that HBV was present in some of the tubules. Electron microscopy revealed wrinkling of glomerular basement membrane with swollen podocytes. Nuclear abnormalities in the form of condensed chromatin and round structures with a dense core surrounded by a clear halo were observed in some of the tubules (Figure 1B and C). This was suggestive of HBV infection.

Tubulo interstitial nephritis (TIN) was attributed to chronic HBV infection, and he was initiated on Entecavir 0.5 mg twice a day. Although the viral DNA load decreased significantly over the next 4 weeks (429 copies/mL, 58 IU/mL), renal function deteriorated (Serum creatinine rose 210 μmol/L eGFR 35 mL/mt). On a repeat renal biopsy, glomeruli showed partial collapse of the tufts with evidence of diffuse tubulo interstitial nephritis. Entecavir was continued. Nine months after initiation of Entecavir, eGFR im-

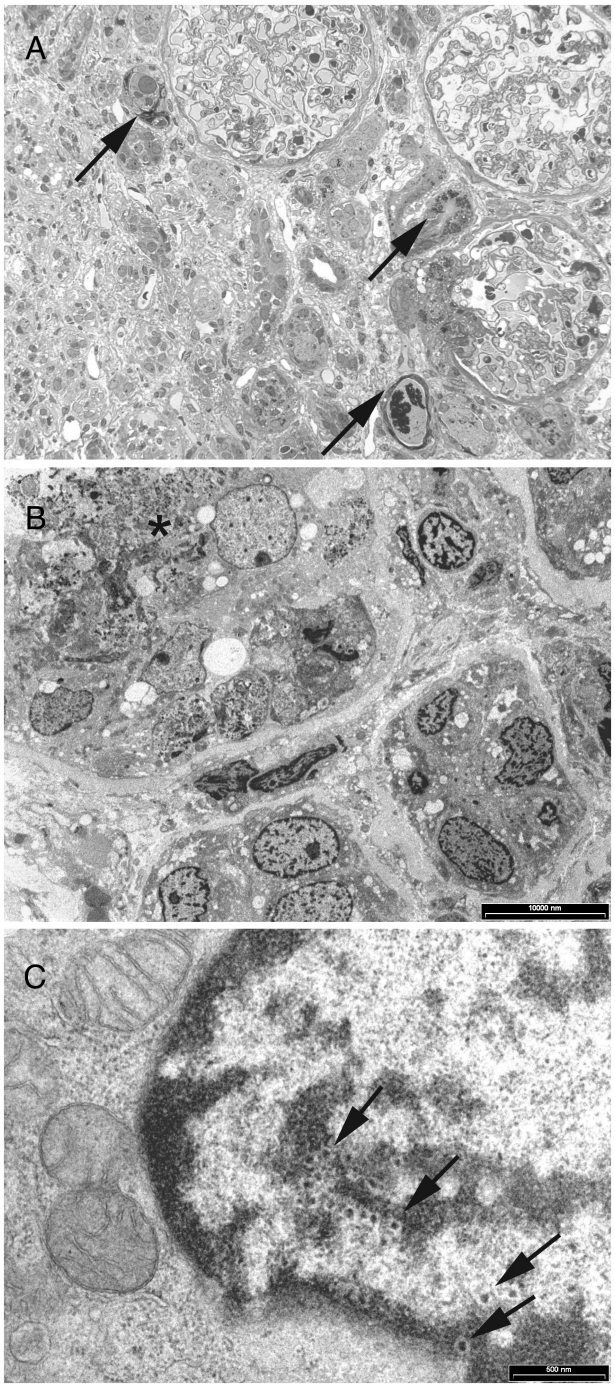

Fig. 1. (**A**) Light microscopy view from the first renal biopsy showing degeneration of tubular epithelium (arrows) and associated interstitial nephritis (LHS of image) ×20; (**B**) electron microscopy showing necrosis of tubular epithelium cells (asterisk), (**C**) virus-like particles in the nucleus of a tubular epithelial cell.

proved to 45 mL/mt (serum creatinine 165 μmol/L) with an undetectable viraemia and normal liver function.

Discussion

Worldwide, more than 400 million people have chronic HBV infection [3]. Extra hepatic manifestations associated with chronic HBV infection can be varied with renal, skin, joint and nervous system manifestations.

Glomerular disease associated with chronic HBV infection was first recognized in 1970 [4]. The renal manifestations of chronic HBV infection usually include glomerulonephritis, essential mixed cryoglobulinaemia and polyarteritis nodosa (PAN) [5]. The most characteristic presentation is nephrotic syndrome, with membranous nephropathy being the most common pathological finding. Children have a good prognosis with up to 95% achieving clinical resolution within 7 years. Resolution is often associated with HBeAg seroconversion [6]. Adults, in contrast, may have a relentless course with 30% progressing to renal failure and 10% eventually requiring haemodialysis. A history of hepatitis usually antedates the renal disease in adults [7].

PAN is a rare complication of chronic HBV infection, occurring in 1% to 5% of patients. Serum HBsAg positivity can be seen in up to 50% of patients with PAN [3]. Our patient did not have PAN as confirmed by a normal CT aortogram.

TIN is a heterogeneous disorder caused by infection, immunological disorders or drugs. Infection by a wide range of organisms is the most common cause of TIN [8]. Human immunodeficiency virus, cytomegalovirus, Epstein–Barr virus, Hanta virus, Polyoma and adenovirus are some of the viruses associated with TIN. We are not aware of any published report of HBV associated TIN in the English literature.

The renal biopsy findings of TIN in our patient were quite unexpected as the usual renal manifestation of HBV nephritis is glomerular. However, the electron microscopic findings of viral structures akin to HBV along with positive immunohistochemical staining for HBV antigen in the tubules, and a progressively worsening renal function with increasing viral load further strengthened our belief of HBV infection as the cause of TIN. Although the majority of patients spontaneously clear the viraemia, active treatment was initiated considering progressive renal impairment. Entecavir, a potent nucleoside analogue with low risk of antiviral resistance, was chosen, as Lamivudine and interferon were considered to be less effective in the presence of very high viral load. Improvement of eGFR with prolonged Entecavir treatment further supports our view that HBV infection is the cause of TIN in this patient.

The exact mechanism of HBV-related renal disease is unclear. An interplay of host, virus and other environmental factors is necessary for nephropathy to develop [5]. This is supported by the observation that only few patients with chronic HBV infection have renal disease. Much of the available evidence points to a direct cytopathic effect by virus, immune complex deposition, viral induced cytokine injury or a specific immunological effector mechanism induced by HBV as probable explanations for renal injury.

In summary, we conclude that, in our patient, TIN was associated with chronic HBV infection. Our conclusions were supported by morphological and clinical evidence. We suggest that TIN should be considered as a possible cause of renal impairment in HBV-infected patients. Our case exemplifies that aggressive antiviral treatment in such patients would stabilize and improve renal function. The

exact pathogenesis of TIN in association with HBV infection needs to be elucidated by future experimental work and further clinical observations.

Conflict of interest statement. None declared.

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