Simultaneous occurrence of hepatitis C virus-associated glomerulonephritis and AL amyloidosis

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Abstract

We report a 65-year-old male with hepatitis C virus (HCV)-associated glomerulonephritis (GN) and AL amyloidosis. This patient had a 14-year history of HCV infection with positive serum HCV RNA at presentation. Diagnosis of HCV-related GN was established using immunohistochemistry in which the HCV-NS3 antigen was mainly detected as granular deposition in glomerular mesangium. AL amyloidosis was determined by electron microscopy, positive Congo red staining and identification of λ-chain in the kidney specimen and monoclonal IgG-λ in serum and urine. Under immunoelectron microscopy, the HCV-NS3 antigen was found in electron-dense deposits, while λ-chains appeared in the amyloid-like filaments.

Keywords: AL amyloidosis; glomerulonephritis; hepatitis C virus

Introduction

HCV not only causes liver diseases, but also is associated with extrahepatic disorders, including cryoglobulinaemia and glomerulonephritis (GN) [1]. Amyloidosis, which shares a common feature of extracellular deposition of pathologic insoluble fibrillar proteins in organs and tissues, is frequently observed in the kidney as a manifestation of systemic amyloidosis [2]. Only a limited number of cases with HCV and AA amyloidosis have been reported in the literature [3,4]. Herein, we report a case of HCV-associated GN and AL amyloidosis, which has not been previously reported to our knowledge.

Case report

In June 2006, a 65-year-old man was admitted to our hospital with a 15-month history of proteinuria and oedema. He was diagnosed with HCV infection in 1992, but did not receive any treatment. Upon admission, the physical examination revealed 3+ pitting oedema on the lower extremities. His blood pressure was 100/60 mmHg. Blood biochemistry tests found decreased levels of serum total protein (53.0 g/L) and albumin (26.3 g/L) with an elevated level of triglycerides (2.06 mmol/L). The erythrocyte sedimentation rate was slightly elevated (20 mm/h), and C3 and C4 were in normal range. Rheumatoid factor and cryoglobulins were negative. The serum anti-HCV antibody was positive and HCV RNA was 3.64 × 10^4 copies/mL with the 1b genotype. Serum and urine immunofixation electrophoresis revealed monoclonal IgG-λ. Proteinuria was 3.6 g/day and urinary sediment revealed microscopic haematuria. Abdominal ultrasonography found mild splenomegaly and normal kidneys. A diagnosis of nephrotic syndrome was established.

A renal biopsy was performed. Under light microscopy, the glomeruli showed mesangial matrix expansion and a thickened glomerular basement membrane (GBM) with amorphous hyaline deposits. There was no glomerular hypercellularity. The walls of some arterioles were thickened with bulky hyaline deposits. The deposits found in the mesangium and arterioles were positively stained by Congo red (Figure 1A), and showed apple-green birefringence with polarized light (Figure 1B). Immunofluorescence microscopy revealed granular staining for IgM and C3 (++) in the mesangium, but no staining for IgG and IgA. Electron microscopy showed 7–10 nm-wide, randomly arranged fibrils in the mesangium and thickened GBM (Figure 2A). The immunohistochemistry revealed granular deposition of the HCV-NS3 antigen in the mesangium (Figure 1C), and the λ light chains in the mesangium and arterioles (Figure 1D). Electron microscopy showed 7–10 nm-wide, randomly arranged fibrils in the mesangium and thickened GBM (Figure 2A).

Treatment started with melphalan 6 mg/day × 7 days and prednisone 60 mg/day × 7 days and was repeated once every month. In addition, α-interferon at a dose of three million units was given three times every week. Ten months later, α-interferon was discontinued when serum HCV-RNA became undetectable. Two years after the therapy, his urine protein was 0.06 g/day with normal
Fig. 1. Histologic and immunohistochemical findings of renal specimens from the patient. (A) Amyloid in the mesangium and arterioles was Congo red positive, magnification ×400. (B) Under polarized light, the Congo red-stained material produced apple-green birefringence, magnification ×200. (C) HCV-NS3 antigen is mainly deposited in mesangial region, magnification ×200, inset ×400. (D) Positive λ light chains deposition, magnification ×400.

Fig. 2. Electron microscopy of the renal specimen and the localization of the HCV-NS3 antigen and λ chains by immunogold labelling. (A) Randomly arrayed fibrils with a diameter of ~7–10 nm in the mesangial region, magnification ×4000, inset ×60 000. (B) Immunostaining with a 5-nm gold-coupled goat anti-mouse IgG that was positive for HCV-NS3 (arrows) and a 10-nm gold-coupled goat anti-rabbit IgG that was positive for λ chains in the mesangial. Gold particles of 5-nm size are mainly located in electron-dense deposits, while 10-nm gold particles are mostly located in the amyloid-like filaments, magnification ×100 000.
serum albumin and creatinine. The blood pressure was 140/70 mmHg. No monoclonal light chain was detected in serum and urine using immunofixation electrophoresis.

Discussion

In this case, the diagnosis of HCV-associated GN was confirmed by immunohistochemistry and immunoelectron microscopy that showed the HCV-NS3 antigen mainly deposited in the glomerular mesangium. Moreover, the response to treatment also supports this diagnosis. In the past decade, the identification of HCV as a cause of mixed cryoglobulinaemia provided convincing evidence for the diagnosis of HCV-associated membranoproliferative GN [5]. However, it is hard to define the diagnostic criterion for other forms of glomerular diseases associated with HCV infection. Undoubtedly, detection of the viral antigens in the kidney would provide direct evidence to support the diagnosis. In our previous study, we found the HCV-NS3 antigen in kidney specimens of 6/21 patients with various glomerular disorders [6]. Sansonno et al. [7], using a panel of monoclonal antibodies, found HCV-specific immunoreactants in kidney biopsy specimens of 8/12 patients with MPGN and cryoglobulinaemia. Based on the above studies, using a panel of stable monoclonal antibodies for detecting HCV antigens in the kidney specimens by the immunohistochemistry or immunoelectron microscopy is recommended for the diagnosis of HCV-associated GN in the future.

The diagnosis of amyloidosis requires histological identification of amyloid deposits. This usually is accomplished by staining with Congo red dye. The Congo red-stained amyloid protein has a salmon pink appearance under light microscopy and produces apple-green birefringence with polarized light. The presence of non-branching, 7–10 nm diameter fibrils under electron microscopy confirms the diagnosis [8]. The pathological features of our case were consistent with these characteristics of amyloidosis. AL amyloidosis in this case was diagnosed based on the positive staining of λ light chains in the kidney specimen and the demonstration of monoclonal IgG bearing λ chains in serum and urine.

In AL amyloidosis, an immunoglobulin light chain or light chain fragment secreted by a single clone of B cells deposits in tissue as amyloid [9]. It is not known whether the single clone of B cells in our case was induced by HCV. In HCV-related cryoglobulinaemia, HCV has been demonstrated to stimulate monoclonal B-cell proliferation through chromosomal rearrangement [10]. It is possible that the proliferation of monoclonal B cells in our case resulted from HCV infection associated with chromosomal rearrangement, which led to the production of amyloid proteins. Further investigation is needed to test this hypothesis.

The prognosis of patients with AL amyloidosis is poor. The median time from diagnosis to dialysis dependence is 14 months and from dialysis to death only 8 months [9]. However, the prognosis of the patient in this case is relatively good. The decrease in his proteinuria paralleled the decrease in his serum HCV-RNA level. After a 2-year follow up, no monoclonal light chain was detected in his serum and urine. The clinical course of this patient supports the hypothesis that renal amyloidosis was induced by HCV infection.

In summary, we report a 65-year-old man with HCV-associated GN and AL amyloidosis. Although the association between HCV and amyloidosis appears to be rare, this possible association should be considered in patients with HCV and nephrotic syndrome because prompt diagnosis and appropriate therapy may prevent organ dysfunction in such cases.

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References


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