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Case Report

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Collapsing glomerulopathy after hepatitis C pegylated interferon treatment. Recovery of renal function with high-dose steroid treatment

Roberto H. Berdichevski[1], Eduardo M. De Carvalho[1], Maria Isabel Edelweiss[2], Luiz Felipe Gonçalves[1] and Roberto C. Manfro[1]

[1]Division of Nephrology, Hospital Mãe de Deus, Porto Alegre, RS, Brazil and [2]Division of Pathology, Hospital de Clínicas de Porto Alegre, RS, Brazil

Correspondence and offprint requests to: Roberto C. Manfro, Ph.D; E-mail: roberto.manfro@maededeus.com.br

Abstract

A patient who developed oliguric acute renal failure and nephrotic syndrome within 2 weeks after finishing interferon and ribavirin treatment is reported. At presentation, HCV PCR was negative, and no immunological laboratory test was found altered. A renal biopsy showed collapsing glomerulopathy, and the patient received supportive haemodialysis and high-dose steroids. Twelve days after steroid treatment, renal function started to recover. After 18 weeks, normal renal function and protein/creatinine urinary ratio were achieved and remained normal up to 1-year post-treatment.

Keywords: acute renal failure; collapsing glomerulopathy; interferon; nephrotic syndrome

Background

Interferon and ribavirin are currently widely used for hepatitis C treatment, and although effective, this therapy is associated with numerous side effects including acute renal failure, focal and segmental glomerulosclerosis (FSGS), and rarely collapsing glomerulopathy (CG) during the treatment course [1]. However, CG has not been reported after treatment discontinuation and resolution of hepatitis C with these drugs. Here, we report on a case of CG that appeared after treatment with interferon and ribavirin and was successfully treated with high-dose steroids. Based on this case, we recommend that the monitoring of renal side effects of INF treatment should be extended for a few months after treatment finishing.

Case report

A 57-year-old white male presented to the emergency room complaining of decreasing urinary output in the last 3 days and referring anuria in the last 24 h. He had no other urinary and obstructive complains, and denied fever, malaise, skin rash or any other symptoms. He denied smoking or alcohol drinking and reported mild hypertension controlled with losartan 50 mg/day.

The relevant information from his previous history was the diagnosis of hepatitis C 11 years before. Seven months before the present condition, he was treated with peginterferon alfa-2a and ribavirin, and the treatment was finished 10 days before his admission. HCV viraemia was negative since the third treatment month. In the physical examination, he was in good general health and well hydrated with normal skin colour. Blood pressure was 140/90 mmHg, heart rate was 80 per minute, temperature was 36.6°C and respiratory rate was 22 breaths/min. In the examination, the only abnormality found was +/4 ankle oedema.

The initial laboratory work-up disclosed normal CBC (haematocrit 40.9%, haemoglobin 14.0 g/dL and 5420 leucocytes). Blood urea nitrogen was 68 mg/dL, serum creatinine was 2.3 mg/dL (increasing to 3.2 mg/dL the following day), serum potassium was 5.7 mg/dL and serum bicarbonate was 21 mEq/mL. Urine examination disclosed 40 red blood cells, ++++ proteins, hyaline and granular casts, and tubular cell debris. The protein/creatinine ratio was 29. Liver function tests, albumin, RNI, C3, C4, P and C ANCA, antinuclear and anti-DNA antibodies, rheumatoid factor, and serum proteinogram were all within the normal range. Anti-hepatitis B virus and anti-HIV were negative, and anti-HCV antibodies were present. Urinary ultrasound disclosed normal sized kidneys and prostate gland without obstruction signs, and a renal biopsy was performed.

He was first found to have anti-HCV antibodies in 1997 and a positive HCV PCR along with altered ALT (180 U/L) and AST (84 U/L) at that time that led to a liver biopsy showing chronic persistent hepatitis. In 2004, a new biopsy disclosed chronic hepatitis with fibrous portal expansion, increased septal lymphocytes and moderate piecemeal necrosis, without iron deposition (Metavir classification A2F2). The virus was found to be 3a genotype, and before treatment onset, the number of viral copies was 33.000 UI/mL. In March 2008, peginterferon alfa-2b

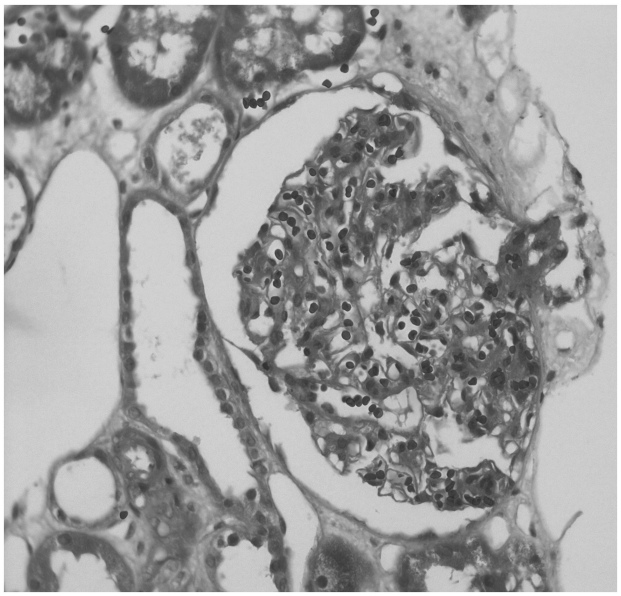

Fig. 1. Digital image of a shrunken glomerulus surrounded by dilated tubuli.

(180 μg/week) and ribavirin (500 mg twice/day) were initiated and kept for 6 months. By the third month of treatment, HCV viral copies were no longer detectable by PCR and remained so until its end. The laboratory work-up upon treatment end disclosed normal LFTs, serum creatinine 0.78 mg/dL, and normal urinary chemistry and sediment.

Before the renal biopsy result was available, the differential diagnosis included rapidly progressive glomerulonephritis and acute vasculitis leading to a methylprednisolone pulse of 1000 mg/day (3 days) followed by prednisone 60 mg/day. In the biopsy, there were 17 glomeruli in the optic microscopy slides, slight mesangial expansion, focal acute tubular necrosis normal vessels and collapsing glomerulopathy (Figure 1). In the immunofluorescence slides, there were 11 glomeruli and absence of immunoglobulins, fibrinogen and complement deposition. At Day 7, after the steroid pulse, urine output started to increase, but he remained dialysis dependent for 12 days. Thereafter, renal function improved continuously reaching a normal serum creatinine and protein/creatinine ratios after 4 and 18 weeks, respectively. Diuresis, serum creatinine, protein/creatinine ratios and steroid doses are shown in Figure 2. Steroids were tapered down over 6 months and discontinued. Renal function and protein/creatinine ratio remained normal thereafter. Also, 12 months after completing the peginterferon plus ribavirin therapy, HCV PCR remained negative.

Discussion

HCV infected patients presenting with acute, sub-acute and chronic renal dysfunction are a common finding in nephrology practice. Most of these patients have immunological phenomena related to virus antigenicity, resulting in immune complex disease, usually membranoproliferative glomerulonephritis with or without cryoglobulinaemia [2]. Viral replication within the glomeruli capillary has also been documented [3], and several patients, with liver disease, also have renal IgA deposits, sometimes leading to IgA nephropathy [4]. In the case reported here, one of these diagnoses was expected, and high-dose steroid therapy was given on clinical grounds of a probable vasculitis/rapidly progressive glomerulonephritis. When the CG diagnosis was made clear by the results of the biopsy, in the absence of HCV replication, the association with peginterferon therapy was suspected.

CG is a relatively new form of glomerular disease that has morphologic pattern characterized by glomerular capillary collapse, severe podocyte injury and glomerular epithelial cell proliferation. Clinically, the hallmarks are marked proteinuria and renal failure [5]. Several mechanisms seem to be involved in the pathophysiology, and the two major described pathways are activation of the immune system and mitochondrial dysregulation. Genetic and environmental factors supposedly play a role in modulating the pathogenetic process. CG is currently classified as a part of FSGS into three major categories: idiopathic, genetic, and secondary or reactive. The last category includes the cases with infections (such as HIV-1, parvovirus B19, cytomegalovirus, malaria, tuberculosis, polyomavirus and others) and medication (interferon-alpha and biphosphonates) [6,7] associated in which the present case should be included. Although some cases of FSGS and CG associated to interferon-alpha have been reported [8], to our knowledge, it is the first case related to peginterferon. The mechanism of interferon-induced podocyte lesion is unknown. Interferon treatment is associated to the development of autoimmune syndromes. The most common described are anti-thyroid antibodies and pancreatic islet cells, resulting in thyroiditis/hypothyroidism and insulin-dependent diabetes [9]. It is conceivable that interferon-induced T-cell activation could lead to podocyte lesion. The observed response to steroid therapy also supports a role for the immune system in the pathogenesis of interferon-induced CG, although some cases of spontaneous resolution have been published [1,10].

Two findings are perhaps peculiar to the presently reported case: first is the presentation of oliguric acute renal failure and nephrotic-range proteinuria after completing anti-HCV therapy, and second is the unreported complica-

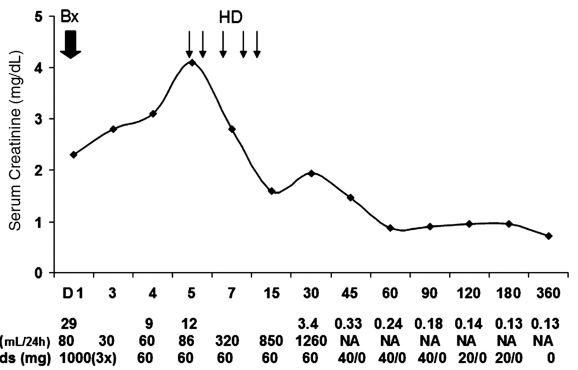

Fig. 2. Illustration of the clinical and laboratory courses. Bx, renal biopsy; HD, haemodialysis; UP/C, urinary protein/creatinine ratio. Steroids, 1000 mg methylprednisolone followed by oral prednisone. Slash means every other day.

tion of peginterferon therapy. Since this therapy is now widely used, it is possible that a number of uncommon adverse effects will arise. In this case, one cannot be sure that an undetected viral infection could have caused the collapsing glomerulopathy. Although possible, we think that the possibility is very weak, due to the absence of clinical and laboratory signs, such as fever and lymphocytosis, that usually accompany acute viral infections. However, in such an unlikely scenario, it is also conceivable that remission could have occurred, as the infection subsides, despite steroid therapy. The prompt exclusion of an infective aetiology and the pathological diagnosis should perhaps direct immediate steroid therapy. One also should consider frequent urinalysis in the follow-up of patients with HCV infection treated with interferon and a nephrology evaluation to be taken as soon as proteinuria is detected and appears on the dipstick.

Conflict of interest statement. None declared.

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