AJKD
Case Report

Recurrent Mixed Cryoglobulinemia Despite Sustained Virologic Response to Treatment: A Case Report

Renuka Chowdhury, MD,[1] and Adrianne Tsen, DO[2]

Cryoglobulinemia is a manifestation of hepatitis C virus (HCV) infection. Treatment of HCV is the mainstay of therapy for mixed cryoglobulinemia syndrome, and newer HCV therapies with direct-acting antiviral agents have achieved great success in treating HCV infection compared with pegylated interferon alfa and ribavirin. Recurrence of mixed cryoglobulinemia syndrome following successful treatment with direct-acting antiviral agents is uncommon, and when it occurs, it is most often due to relapse of HCV viremia. We report a case of recurrent mixed cryoglobulinemia syndrome following HCV treatment with a new direct-acting antiviral agent (sofosbuvir) and ribavirin, in which HCV RNA was undetectable in serum, but detectable in the cryoprecipitate. *Am J Kidney Dis.* 70(2):301-304. © *2017 by the National Kidney Foundation, Inc.*

INDEX WORDS: Recurrent mixed cryoglobulinemia syndrome; hepatitis C virus (HCV); direct antiviral agents; cryoprecipitate; sustained virological response (SVR); sofosbuvir; kidney biopsy; membranoproliferative glomerulonephritis; HCV RNA; viral load; renal involvement; case report.

Hepatitis C virus (HCV) infection primarily affects the liver. In 70% to 85% of patients, HCV infection becomes a chronic illness, which may progress to cirrhosis and hepatocellular carcinoma. However, in 38% to 76% of patients, extrahepatic autoimmune manifestations may develop in the form of mixed cryoglobulinemia, Sjögren syndrome, autoimmune thyroiditis, and other B-cell lymphoproliferative disorders.[1,2]

Approximately 90% of mixed cryoglobulinemia syndromes are associated with HCV infection.[3] Renal involvement occurs in 20% of patients with mixed cryoglobulinemia syndrome, and type I membranoproliferative glomerulonephritis is the most predominant histologic pattern found. Eradication of the HCV most often results in resolution of the mixed cryoglobulinemia syndrome.

New oral therapies for HCV infection, known as direct-acting antiviral agents, are now being used with great success, with a sustained viral response being achieved in >90% of patients with HCV mixed cryoglobulinemia syndrome by week 12 of treatment.[3] The new direct-acting antiviral agent sofosbuvir is a nucleotide analogue polymerase inhibitor that targets the nonstructural protein 5B RNA-dependent RNA polymerase and terminates viral replication.

We report a case of recurrent mixed cryoglobulinemia in a patient with undetectable HCV RNA following successful treatment of HCV infection with sofosbuvir and ribavirin. To our knowledge, this is the first published report of recurrent mixed cryoglobulinemia syndrome following successful treatment of HCV infection with a new direct-acting antiviral agent in which HCV RNA was undetectable in serum, but detectable within the cryoprecipitate.

CASE REPORT

A 63-year-old man presented with severe bilateral lower-extremity edema extending up to the abdomen, nephrotic-range proteinuria, and hematuria, which led to an extensive serologic workup and kidney biopsy. Serum creatinine level was 0.8 mg/dL, corresponding to estimated glomerular filtration rate > 60 mL/min/1.73 m^2 as calculated using the MDRD (Modification of Diet in Renal Disease) Study equation. HCV RNA testing in serum identified genotype 2b, at a titer of 7,200,000 IU/mL. He had hypocomplementemia, and cryoglobulins were detected in serum (Fig 1).

Kidney biopsy (images available in Item S1) showed 13 glomeruli with mesangial hypercellularity, increased glomerular lobularity, and endocapillary proliferation. Hyaline thrombi were identified within glomeruli. No acute tubular injury, glomerular sclerosis, or vasculitis was noted. Electron microscopy showed a variable degree of visceral foot-process effacement, mesangial hypercellularity, and increased mesangial matrix. Rare subendothelial electron-dense deposits and extensive mesangial interposition was also noted. Immunofluorescence was positive for immunoglobulin G (IgG) and C3c (trace to 1+), but negative for IgA, IgM, C1q, and κ and λ light chains. The final diagnosis was cryoglobulinemic HCV-associated membranoproliferative glomerulonephritis.

The patient received 6 cycles of cyclophosphamide (850 mg each) and initial high-dose intravenous methylprednisolone followed by oral prednisone taper. He was also referred to a hepatologist and went on to complete 3 months of antiviral therapy with sofosbuvir and ribavirin (Fig 1). His kidney function was

From the [1]Dallas Nephrology Associates, Dallas, TX; and [2]University of Texas Health Science Center at San Antonio, San Antonio, TX.

Received April 22, 2016. Accepted in revised form January 3, 2017. Originally published online March 23, 2017.

Address correspondence to Renuka Chowdhury, MD, Dallas Nephrology Associates, 1150 N Bishop Ave, Ste 100, Dallas, TX 75063. (e-mail: chowdhuryr@dneph.com) or Adrianne Tsen, DO, 5623 Hamilton Wolfe, Apt 712, San Antonio, TX 78240. (e-mail: adriannetsen@gmail.com)

0272-6386
http://dx.doi.org/10.1053/j.ajkd.2017.01.041

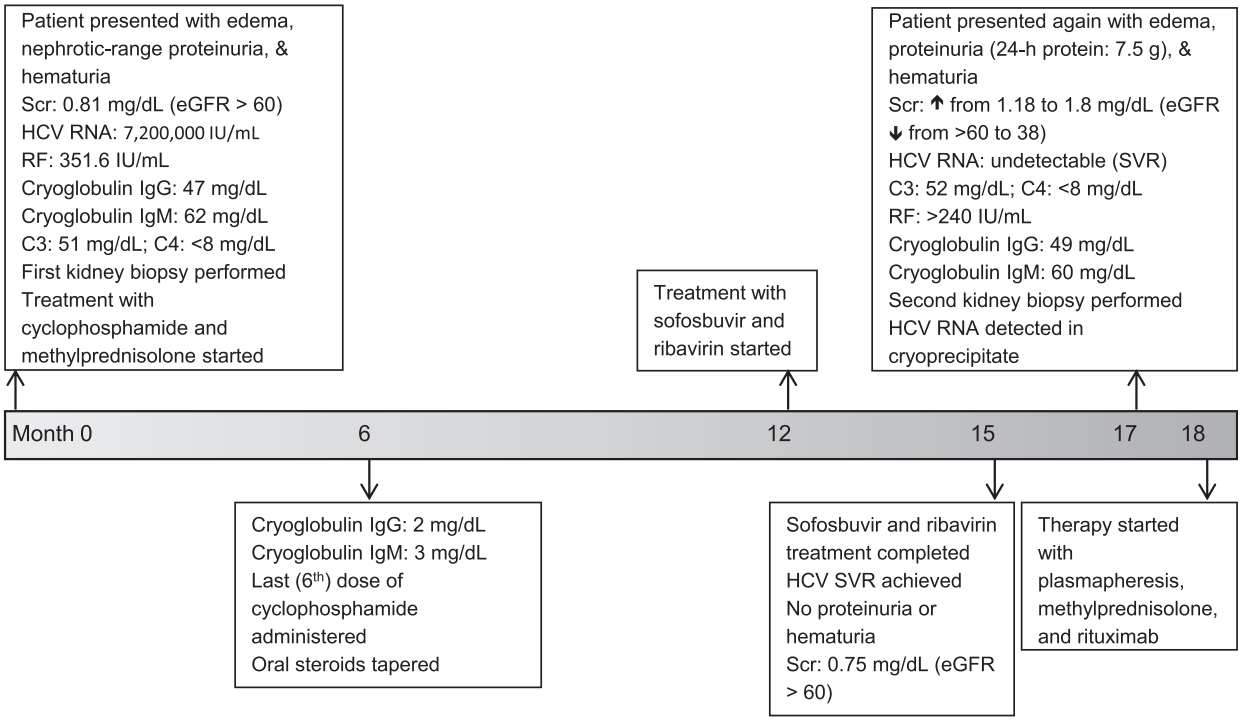

Figure 1. Timeline of the clinical course. Normal ranges: C3: 88-165 mg/dL; C4: 14-44 mg/dL; RF: <12 IU/mL, Creatinine: 0.7-1.4 mg/dL, eGFR: >60 ml/min/1.7m^2 BSA (MDRD study equation). Abbreviations: eGFR, estimated glomerular filtration rate (in mL/min/1.73m^2); HCV, hepatitis C virus; IgG, immunoglobulin G; RF, rheumatoid factor; Scr, serum creatinine; SVR, sustained virologic response.

stable (no proteinuria or hematuria; serum creatinine level, 0.75 mg/dL; estimated glomerular filtration rate > 60 mL/min/1.73 m^2) and he was noted to have a sustained virologic response.

About 17 months after the initial presentation, the patient visited the emergency department with worsening hypertension and progressive lower-extremity edema. Urinalysis was significant for proteinuria (protein excretion, 7.5 g/d) and hematuria. Serum creatinine level increased from 1.2 to 1.8 mg/dL, corresponding to decline in estimated glomerular filtration rate from >60 to 38 mL/min/1.73 m^2. He was noted to have hypocomplementemia, and cryoglobulins were detected in serum. Serologic workup (for antinuclear antibody, antineutrophil cytoplasmic antibody, anti–glomerular basement membrane antibody, anti-SS-A/Ro, and anti-SS-B/La) was unremarkable. Epstein-Barr virus (EBV) testing detected anti-EBV IgG but not anti-EBV IgM; HCV RNA was undetectable in serum. A normal CT of the chest, abdomen, and pelvis and a normal bone marrow biopsy ruled out lymphoproliferative disorders.

Kidney biopsy (images in Item S1) demonstrated 14 glomeruli, 2 of which were globally sclerosed. There was increased mesangial matrix but no significant tubular atrophy, interstitial expansion, vasculitis, or thrombosis. Rare hyaline thrombi were noted within glomerular capillary lumina. Electron microscopy demonstrated epithelial foot-process effacement, hypercellular mesangium with increased matrix, thickening of glomerular basement membranes, and focal subendothelial electron-dense deposits with mesangial interposition. Immunofluorescence was positive for IgM (trace), C3c (trace to 1+), and κ light chains (trace); IgG, IgA, C1q, and λ light chains were negative. The pathologist did not find a significant difference in the specimen from this second kidney biopsy compared to the first.

The patient received high-dose intravenous methylprednisolone for 3 days, after which he was switched to oral prednisone. Due to the severity of the patient's nephrotic syndrome and worsening kidney function, the patient was started on plasmapheresis on day 4 of admission and scheduled to undergo plasmapheresis every other day for 2 weeks. On day 11 of admission, the patient was given rituximab, 500 mg, and was scheduled to receive it once weekly for 3 more weeks.

DISCUSSION

In 1966, Meltzer et al[4] discovered cryoglobulins, and in 1974, cryoglobulins were classified into 3 types: types I, II, and III. Type I cryoglobulins are associated with paraproteinemias. Although HCV infection may be the most common cause of type II cryoglobulinemia, hepatitis B virus and EBV infection have also been implicated. Type III cryoglobulinemia is seen in association with HCV infection, systemic lupus erythematous, systemic sclerosis, and lymphoproliferative disorders.[4,5]

The mechanism by which mixed cryoglobulinemia syndrome occurs in association with HCV infection is not well understood. However, recent studies suggest that cytokines and chemokines (eg, CXCL11) may play an important role in the immune response to HCV.[6]

Another theory proposes that B-cell proliferation eventually reaches an autonomous phase and becomes HCV independent, as evidenced by the persistence of monoclonal immunoglobulin gene rearrangement after complete HCV treatment.[7-9]