Clinical Kidney Journal, 2019, vol. 12, no. 3, 362–364

doi: 10.1093/ckj/sfy055
Advance Access Publication Date: 9 July 2018
Exceptional Case

EXCEPTIONAL CASE

Mixed cryoglobulinaemia vasculitis after sustained hepatitis C virological response with direct-acting antivirals

Diego Barbieri, Ana García-Prieto, Esther Torres, Eduardo Verde, Marian Goicoechea and José Luño

Department of Nephrology, Hospital General Universitario Gregorio Marañón, Madrid, Spain

Correspondence and offprint requests to: Diego Barbieri; E-mail: diego.barbieri.merlo@gmail.com; Twitter handle: @DrChipi_MD

ABSTRACT

Mixed cryoglobulinaemia (MCG) is one of the most severe extrahepatic hepatitis C virus (HCV)-associated complications, and could involve several organs, including the kidney. MCG prognosis relies on HCV response to antiviral treatment and has changed over the last years, especially after the introduction of new direct acting antivirals (DAA). MCG persistence despite sustained virological response (SVR) is uncommon and has a poorly known meaning and prognosis. We report a case of a patient with chronic HCV infection treated with DAA who developed MCG vasculitis despite the SVR.

Keywords: direct-acting antivirals, hepatitis C virus, membranoproliferative glomerulonephritis, mixed cryoglobulinaemia vasculitis, sustained virological response

INTRODUCTION

Hepatitis C virus (HCV) is known for its hepatic and extrahepatic manifestations. Mixed cryoglobulinaemia (MCG) is one of the most severe complications in which cryoglobulins can deposit and produce vasculitis (mixed-cryogobulinemic vasculitis, MCGVasc) [1] causing palpable purpura, arthralgias, glomerulonephritis or neuropathy.

During the interferon–ribavirin (IFN+RBV) era, the HCV-related MCG prognosis relied on viral response [2]. After the introduction of new direct acting antivirals (DAAs), sustained virological response (SVR) and MCGVasc have shown discordant rates [3]. Its significance and prognosis are still uncertain [4].

We report the case of a patient with HCV-related MCG who developed a systemic vasculitis after SVR with DAAs.

CASE REPORT

A 61-year-old man from Equatorial Guinea with a previous history of resistant hypertension and chronic active HCV infection was referred to our Nephrology Department to assess non-nephrotic-range proteinuria and microhaematuria. He was asymptomatic and had normal liver function. Complementary tests revealed the presence of serum type II polyclonal cryoglobulins, positive rheumatoid factor (RF) and complement consumption, with negative anti-nuclear antibodies (ANA), (Anti-double stranded DNA (Anti-dsDNA) antibodies and Extractable Nuclear Antigens (ENA) (Figure 1).

An immunocomplex-mediated membranoproliferative glomerulonephritis (MPGN) was the assumed diagnosis and DAAs treatment was initiated with sofosbuvir and ledipasvir.

Received: 17.11.2017; Editorial decision: 24.5.2018

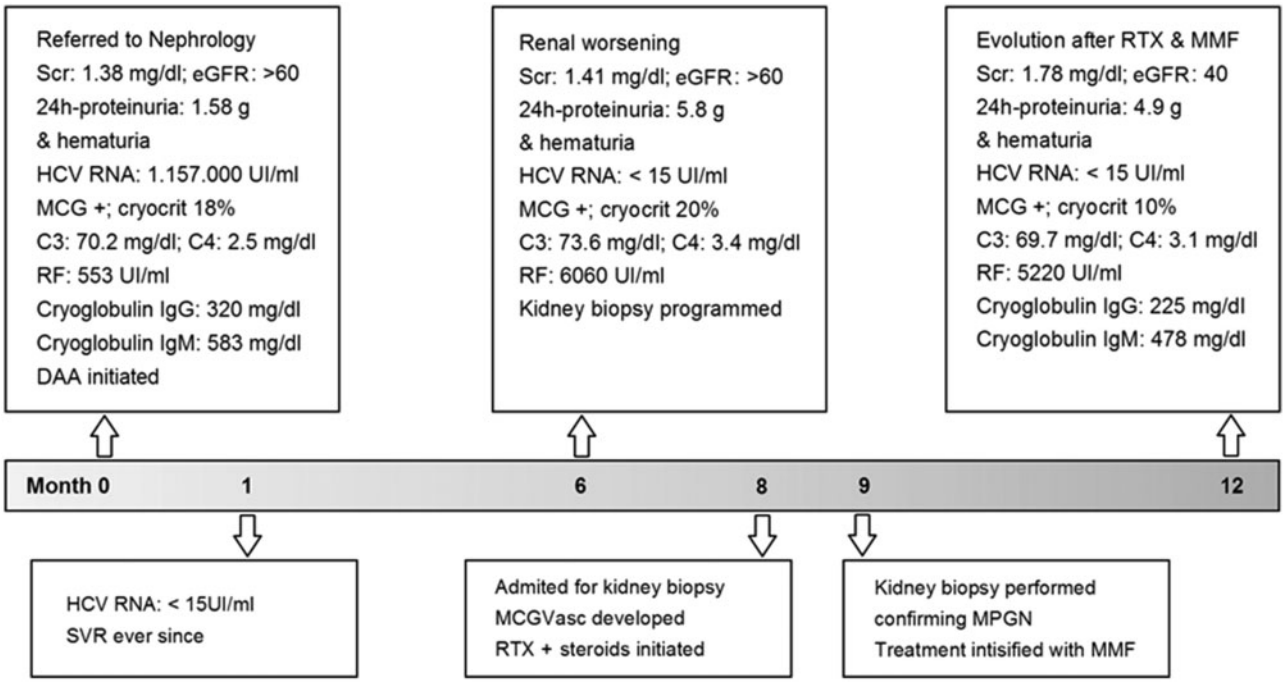

FIGURE 1: Timeline of the clinical course. eGFR, estimated glomerular filtration rate (in mL/min/1.73 m^2); RTX, rituximab; Scr, serum creatinine.

After 4 weeks of treatment, polymerase chain reaction (PCR) for HCV became negative and SVR was achieved ever since. However, in the following 6 months, the patient developed a nephrotic syndrome without renal impairment. Persistent type II cryoglobulins were detected with complement consumption still ongoing. Tests for HCV (including hepatitis C virus (HCV)-polymerase chain reaction (PCR) in cryoprecipitate), hepatitis B virus (HBV), human immunodeficiency virus (HIV), Epstein–Barr virus and inflammatory diseases (ANA, ENA, anti-DNA ds, etc.) were negative.

A kidney biopsy was scheduled and the patient was admitted asymptomatic, but he abruptly developed right 7th and 12th cranial nerve paralysis. Magnetic resonance revealed cerebral microhaemorrhages suggestive of small-vessel vasculitis. Steroids and rituximab were started the day after. A bone marrow biopsy was performed within the admission which reported a marginal type non-Hodgkin lymphoma (NHL).

After 4 weeks, once the patient was stabilized, a renal biopsy was performed that showed a membranoproliferative pattern with immunoglobulin G (IgG), immunoglobulin M (IgM) and C3 deposits. Nephrotic-range proteinuria and haematuria persisted, so the immunosuppressant therapy was intensified with mycophenolate mofetil (MMF), with reduction of cryocrit values but without renal response.

DISCUSSION

HCV is well known for having high immunogenic capacity, converting HCV infection in a systemic disease. HCV-related MCG is a severe extrahepatic complication. It is usually type II, with a polyclonal IgG, monoclonal IgM (RF) and cryocrit around 5–10% [1, 3]. MCGVasc is a small-vessel vasculitis due to cryoglobulin deposition.

In the pre-DAAs era there was a strong correlation between SVR and MCG remission. IFNa+RBV achieved SVR rates around 40–60%, with MCGVasc remission in >70% of cases [2]. Introduction of DAAs resulted in improved SVR rates, >90% [3]. However, MCGVasc response rate in these patients is highly variable [4].

In our case, renal involvement was the first manifestation of MCGVasc and led to initiation of DAAs. SVR was rapidly achieved, but there was no renal response. Instead, a potentially life-threatening vasculitis was developed. Other aetiologies for persistent MCG were ruled out, including HCV reactivation, infections and rheumatological diseases. Bone marrow biopsy showed a marginal lymphoma, which is a low aggressive NHL. Since in our case cryoglobulinaemia has a clear polyclonal IgG component we believe that the presence of this lymphoma is the consequence of MCG and not its cause. Thus, we found no explanation for persistent MCGVasc in our patient.

Rituximab and steroids were initiated, with neurological improvement but without renal or immunological response. Thus, the treatment was intensified with MMF with slight immunological amelioration but with persistent nephrotic-range proteinuria and haematuria (Figure 1).

Different aetiopathogenic hypothesis have been proposed for the persistent cryoglobulins in cases like this, such as the absence of immunomodulatory treatment, decreased immunocomplex clearance due to liver failure or 'immunological no-return points' [4]. Another hypothesis is an occult HCV infection (OCI), defined as positive HCV Ribonucleic acid (RNA) in hepatic biopsy or blood macrophages with negative serum PCR [5]. Persistent MCG with aggressive presentation as MCGVasc despite SVR raises the OCI hypothesis as a possible aetiology in our case.

In conclusion, HCV-related MCG prognosis has undergone great changes since DAAs introduction, creating a new subpopulation of patients with SVR and persistent MCGVasc without known cause. Further studies are required to clarify the aetiopathogenesis and long-term prognosis in this population.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Saadoun D, Thibault V, Si Ahmed SN *et al*. Sofosbuvir plus ribavirin for hepatitis C virus-associated cryoglobulinaemia vasculitis: VASCUVALDIC study. *Ann Rheum Dis* 2016; 75: 1777–1782
2. Gragnani L, Fognani E, Piluso A *et al*. Long-term effect of HCV eradication in patients with mixed cryoglobulinemia: a prospective, controlled, open-label, cohort study. *Hepatology* 2015; 61: 1145–1153
3. Sise ME, Bloom AK, Wisocky J *et al*. Treatment of hepatitis C virus-associated mixed cryoglobulinemia with direct-acting antiviral agents. *Hepatology* 2016; 2: 408–417
4. Cornella SL, Stine JG, Kelly V *et al*. Persistence of mixed cryoglobulinemia despite cure of hepatitis C with new oral antiviral therapy including directacting antiviral sofosbuvir: a case series. *Postgrad Med* 2015; 127: 413–417
5. Attar BM, Van Thiel D. A new twist to a chronic HCV infection: occult hepatitis C. *Gastroenterol Res Pract* 2015; 2015: 579147