



Cryoglobulinemic vasculitis and membranoproliferative glomerulonephritis in a patient with cured virus C infection

Vasculitis crioglobulinémica y glomerulonefritis membranoproliferativa en paciente con infección por virus C curada

Dear Editor,

The development of new direct-acting antivirals (DAA) for the treatment of hepatitis C virus (HCV) has been a revolution in the control of this infection, achieving sustained virological response (SVR) rates close to 99%.^{1–4} Some extra-hepatic (EH) manifestations associated with this infection may persist or recur after achieving SVR with DAA.⁴ Few cases have been reported of the development of new EH manifestations after achieving SVR. We present a case of mixed cryoglobulinaemic vasculitis (MCV) and membranoproliferative glomerulonephritis, accompanied by sicca syndrome (SS), which manifested 28 months after achieving SVR with DAA.

This patient was a 70-year-old woman with HCV infection without liver or EH involvement, treated with elbasvir/grazoprevir in December 2017, achieving SVR. Six months after achieving undetectable viraemia, she began to experience xerophthalmia, xerostomia and parotitis, for which she began follow-up by rheumatology. Blood tests showed: hypergammaglobulinaemia (polyclonal IgG), positive ANA (titre 1/640), negative anti-RO antibodies (anti-Ro) and anti-La antibodies (anti-LA), rheumatoid factor (RF) 55 mg/dl (0–40); serum creatinine (sCr) 0.87 mg/dl; basic urine negative for proteins and red blood cells. With these abnormalities, she was diagnosed with SS, as she did not meet the criteria for primary Sjögren's syndrome due to negative anti-Ro and anti-La, and previous HCV infection.

In January 2020, the patient began to experience purpuric skin lesions on her lower limbs associated with type III or mixed positive cryoglobulins (polyclonal IgG and polyclonal IgM), without prior testing having been performed; her RF had risen (130 IU/mL) and renal function remained normal (sCr 0.87 mg/dl), along with a basic urine sample with no abnormalities. Skin biopsy was inconclusive. However, based on the rest of results, it was treated as type III or mixed cryoglobulinaemic vasculitis with skin involvement and she was started on oral prednisone (0.5 mg/kg/day).

In May of that same year, she was admitted for a respiratory infection, documenting simultaneously a clinical and bio-

chemical nephrotic syndrome (sCr 1.35 mg/dl; urea 55 mg/dl; albumin 3.2 g/dl; cholesterol 275 mg/dl; 24-h urinary protein 5,900 mg/24 h; urinary sediment with 5–10 dysmorphic red blood cells/field, and hypocomplementaemia with C3 of 47.80 mg/dl and C4 of 2.20 mg/dl). The rest of the autoimmunity study was negative (negative antiPLA2R, ANCA and proteins). Kidney biopsy showed 18 glomeruli, all of them hypertrophic with lobulated morphology and occlusion of vascular lumens by inflammatory cells, mesangial expansion with mesangial hypercellularity (Fig. 1A and B). Using the silver technique, double contour images in the capillary loops (Fig. 1C). Immunofluorescence showed capillary positivity for IgG (+++) in a coarse granular pattern and with a subendothelial and mesangial location (Fig. 1D). All of this is consistent with a pattern of membranoproliferative glomerulonephritis (MPGN) mediated by immune complexes.

Although there was no sample for electron microscopy and no thrombi or fibrinoid necrosis were found, the rest corresponded to type III MCV with skin and kidney involvement in the form of MPGN, probably related to past HCV infection. A lymphoproliferative syndrome was ruled out by computed tomography, and the HCV viral load was always negative. The patient was given rituximab (500 mg x 2 doses 15 days apart) and steroid therapy in a tapering regimen. After three months she was in complete remission: sCr 0.8 mg/dl; albumin 4.2 g/dl; C3 66.90 mg/dl (normal); C4 5.40 mg/dl (normal); negative cryoglobulins. Urinalysis with 24-h urinary protein of 294 mg/g and normal sediment. She has remained stable over the subsequent 18 months of follow-up, receiving maintenance doses of rituximab (500 mg) every six months since then.

The development of new DAA against HCV has represented a paradigm shift in the treatment of this infection.¹ They are clearly effective in eradicating the virus, with SVR rates close to 99%. Despite this, the effectiveness in controlling some EH manifestations is not so evident.¹

MCV is the most common EH manifestation.² Typically, those associated with hepatitis C virus infection are type II and/or type III cryoglobulinaemia, also known as mixed cryoglobulinaemias.³ Some 70–90% are associated with HCV infection.² In our case, it was a type III mixed cryoglobulinaemia because it was formed by polyclonal IgG and IgM, with rheumatoid activity.

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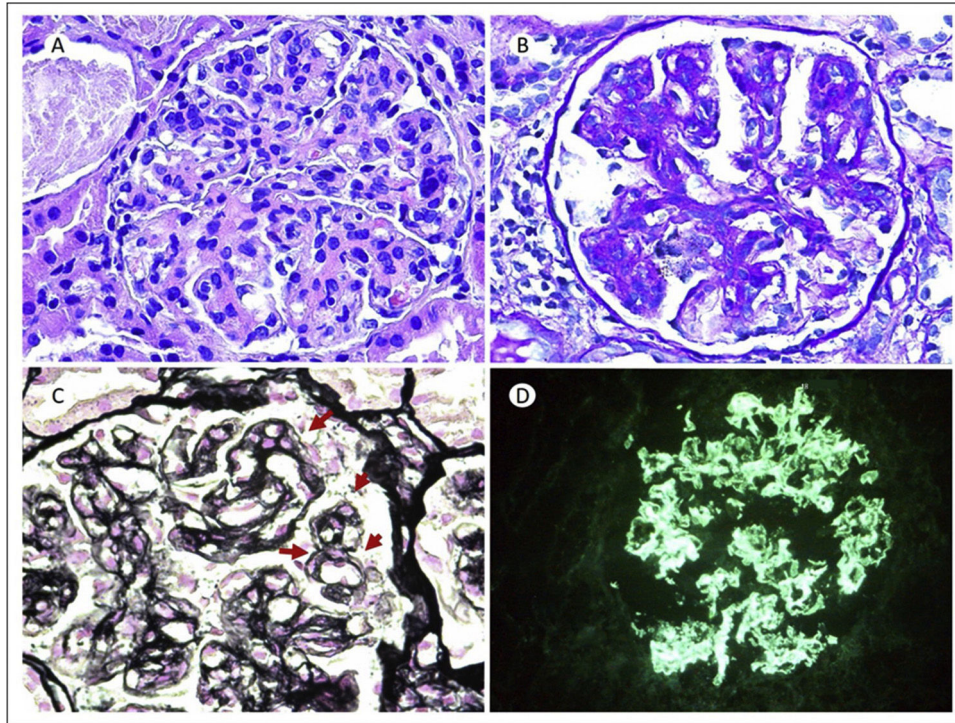


Fig. 1 – (A) H&E: 20×. Glomerulus with lobulated morphology, mesangial expansion due to matrix and mesangial and endocapillary proliferation. (B) PAS 20×: PAS positive mesangial expansion, with increased cellularity. (C) Methenamine silver 64×. Images of double contours in the glomerular capillary loops (red arrows). (D) Direct immunofluorescence (DIF) IgG 20×. Intense deposit (3+) in a coarse granular pattern and with a subendothelial and mesangial location for IgG.

The renal involvement usually associated with MCV due to hepatitis C virus is MPGN.³ DAA have highly variable clinical and immunological response rates on MCV (64%–96% and 48%–89%, respectively).⁴ Furthermore, some authors have suggested that the use of DAA alone could be insufficient in controlling renal manifestations and cryoglobulinaemic vasculitis.⁴ Recent publications have reflected persistence of MCV with or without renal involvement despite SVR with DAA.^{5–8} In these patients, the use of immunosuppressive treatment such as rituximab can be effective in controlling the disease.⁹ In our case, what makes it unusual is that the manifestations appeared after SVR. Prior to treatment with DAA, no EH involvement had been documented. To the best of our knowledge, there are few published cases similar to ours.

The mechanism by which patients with eradicated HCV infection can develop EH manifestations after treatment with DAA is not fully understood. HCV infection causes different immune system regulation abnormalities. One well-known theory is that HCV settles inside the cell it infects, thereby avoiding attack by the immune system.¹⁰ HCV acts on the usual cellular DNA repair mechanisms, producing an increase in unrepaired DNA alterations that are associated with greater genomic instability, increasing the risk of development of neoplasia and dysfunction of the immune system.^{10,11} Among other factors, this would cause the abnormal activation of B lymphocytes and their monoclonal expansion, which would give rise to the formation of cryoglobulins responsible for MCV.¹¹ Some studies have found that patients who achieved

clinical remission of MCV after the use of DAA have shown a decrease in activated B lymphocytes and an increase in regulatory T lymphocytes.¹² Other authors, such as Hegazy et al., have found that patients with HCV infection treated with DAA have a higher concentration of B lymphocyte activation factors (BAFF and APRIL) during the first 12 months after receiving treatment.¹³ This could lead to hyperactivity of B lymphocytes after the use of DAA, which could explain the appearance of autoimmune manifestations after treatment.

Lastly, contrary to what might have happened with the immunomodulatory effect of interferon, free regimens of this drug could lose this anti-inflammatory effect, and not be sufficient in all cases to control EH manifestations.¹³

In conclusion, DAA improve hepatic morbidity and mortality rates in almost all cases. The exact mechanism behind the development of autoimmune manifestations that appear once SVR is achieved with these drugs is unknown. Therefore, in the first few months after treatment with DAA, it is important to closely monitor for autoimmune manifestations as, if they do appear, they may require additional immunosuppressive therapy.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

REFERENCES

- Manns MP, Buti M, Gane E, Pawlotsky JM, Razavi H, Terrault N, et al. Hepatitis C virus infection. *Nat Rev Dis Primers*. 2017;3:17006.
- Cacoub P, Comarmond C, Domont F, Savey L, Saadoun D. Cryoglobulinemia vasculitis. *Am J Med*. 2015;128(9):950–5.
- Sethi S, Fervenza FC. Membranoproliferative glomerulonephritis—a new look at an old entity. *N Engl J Med*. 2012;366(12):1119–31.
- Santoriello D, Pullela NK, Uday KA, Dhupar S, Radhakrishnan J, D'Agati VD, et al. Persistent hepatitis C virus-associated cryoglobulinemic glomerulonephritis in patients successfully treated with direct-acting antiviral therapy. *Kidney Int Rep*. 2018;3(4):985–90.
- Obrîșcă B, Jurubiță R, Sorohan B, Iliescu L, Baston C, Bobeică R, et al. Clinical outcome of HCV-associated cryoglobulinemic glomerulonephritis following treatment with direct acting antiviral agents: a case-based review. *Clin Rheumatol*. 2019;38(12):3677–87.
- Ghosn M, Palmer MB, Najem CE, Haddad D, Merkel PA, Hogan JJ. New-onset hepatitis C virus-associated glomerulonephritis following sustained virologic response with directacting antiviral therapy. *Clin Nephrol*. 2017;87(5):261–6.
- Sollima S, Milazzo L, Peri AM, et al. Persistent mixed cryoglobulinaemia vasculitis despite hepatitis C virus eradication after interferon-free antiviral therapy. *Rheumatology*. 2016;55:2084–5.
- Chowdhury R, Tsen A. Recurrent mixed cryoglobulinemia despite sustained virologic response to treatment: a case report. *Am J Kidney Dis*. 2017;70:301–4.
- Kaegi C, Wuest B, Schreiner J, Steiner UC, Vultaggio A, Matucci A, et al. Systematic review of safety and efficacy of rituximab in treating immune-mediated disorders. *Front Immunol*. 2019;10:1990.
- Flores-Chávez A, Carrion JA, Forns X, Ramos-Casals M. Extrahepatic manifestations associated with Chronic Hepatitis C Virus Infection. *Rev Esp Sanid Penit*. 2017;19(3):87–97.
- Terrier B, Joly F, Vazquez T, Benech P, Rosenzweig M, Carpentier W, et al. Expansion of functionally anergic CD21-/low marginal zone-like B cell clones in hepatitis C virus infection-related autoimmunity. *J Immunol*. 2011;187(12):6550–63.
- Comarmond C, Garrido M, Pol S, et al. Direct-acting antiviral therapy restores immune tolerance to patients with hepatitis C virus-induced cryoglobulinemia vasculitis. *Gastroenterology*. 2017;152:2052–62.
- Mediterranean Consortium for the study of Cryoglobulinemic Vasculitis Hegazy MT, Allam WR, Hussein MA, Zoheir N, Quartuccio L, El-Khamisy SF, et al. Increased genomic instability following treatment with direct acting anti-hepatitis C virus drugs. *EBioMedicine*. 2018;35:106–13.

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Decision making – Should we perform kidney transplantation on a patient with a positive RT-PCR test for SARS-CoV-2?

Toma de decisiones - ¿Debería realizarse un trasplante de riñón a un paciente con una prueba RT-PCR positiva para SARS-CoV-2?

Dear Editor:

The COVID-19 pandemic brought new challenges to daily decision-making in Kidney Transplant (KT) Centers. Excluding infection with SARS-CoV-2 virus before patients undergo KT

became a routine due to the significant prevalence of asymptomatic infection. According to the Centers for Disease Control and Prevention (CDC), people who recovered from COVID-19 may have prolonged detection of SARS-CoV-2 RNA, without being at risk of disease transmission. Studies have indicated that patients who were hospitalized and recovered may have detectable SARS-CoV-2 RNA in the upper respiratory tract up to 3 months after symptom onset.¹ In some cases, a KT was already performed after recovery but within this timeframe.²

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