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CASE REPORT | LIVER

Relapse of HCV Genotype 1b Infection After Sofosbuvir/Ledipasvir Treatment Presenting as De Novo Cryoglobulinemic Vasculitis

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ABSTRACT

Relapse of hepatitis C virus (HCV) genotype 1 infection after combination therapy with sofosbuvir and ledipasvir is unusual. We report a treatment-naïve, non-cirrhotic patient in whom the relapse of genotype 1b HCV infection was accompanied by de novo cryoglobulinemic vasculitis and glomerulonephritis, requiring hemodialysis for acute renal failure. Sequence analysis revealed several resistance-associated variants in the HCV *NS5a* gene but not in *NS3/4A*. The patient's vasculitis was successfully treated with immunosuppression and plasmapheresis, followed by retreatment of HCV with a combination of sofosbuvir, simeprevir, and ribavirin. The patient achieved sustained virological response, recovered his renal function, and remains in remission from cryoglobulinemia.

INTRODUCTION

Chronic hepatitis C virus (HCV) affects 170 million individuals worldwide, with ~60% being infected with genotype 1.[1] Although most patients are asymptomatic, untreated disease can result in cirrhosis, hepatocellular carcinoma, and extrahepatic complications including cryoglobulinemia. Cryoglobulinemia is a vasculitic syndrome characterized by immune complexes that reversibly precipitate at low temperatures. Development of cryoglobulinemia correlates with HCV duration, and the cornerstone of management is anti-HCV therapy. The advent of direct-acting antiviral (DAA) agents, with unprecedented response rates and rare relapses, would be expected to reduce the impact of this complication.

CASE REPORT

A 67-year-old man with a past history of hypertension, hyperlipidemia, diabetes, and chronic kidney disease presented for re-evaluation of chronic HCV, diagnosed 25 years earlier. Risk factors included past blood transfusions and a needle-stick injury involving a non-A, non-B hepatitis patient. He was treatment-naïve. On initial evaluation, he was asymptomatic and examination was unremarkable. Laboratory testing revealed elevated transaminase levels and HCV genotype 1b with a viral load of 1,322,216 IU/mL. Transient elastography revealed a score of 27 kPa, suggestive of advanced fibrosis. The patient was treated with a 12-week course of sofosbuvir (400 mg daily) and ledipasvir (90 mg daily). The treatment course was uneventful, with rapid normalization of transaminase levels and clearance of the virus.

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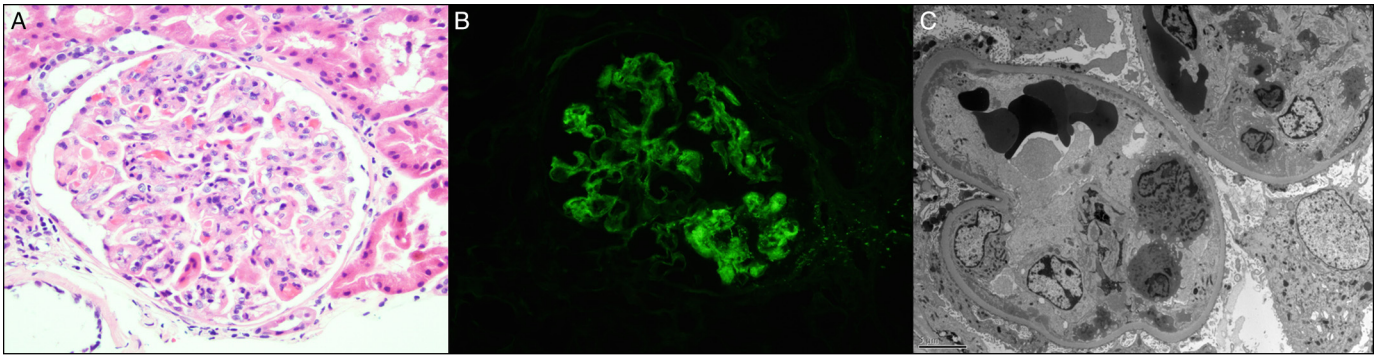

Figure 1. (A) Hematoxylin and eosin (H&E) stain demonstrating a glomerulus with a lobulated appearance, many lamellae containing scattered neutrophils, and prominent eosinophilic globules within capillary lumens. (B) Direct immunofluorescence demonstrating >2 coarse depositions of antibodies to IgG within the mesangium and capillary loops as well as focal staining of luminal plugs. (C) Ultrastructural examination revealing numerous immune-type subendothelial deposits.

Three months after completing treatment, the patient presented with flu-like symptoms, vomiting, and diarrhea. No skin rash was noted. Laboratory testing showed elevated liver enzymes and acute kidney injury (creatinine 2.3 mg/dL). Rheumatoid factor (RF) levels were elevated, and complement proteins (C3, C4) were decreased. A cryoglobulin test was positive, with a combination of polyclonal immunoglobulin (Ig) G immunoglobulins and elevated RF, which confirmed type II cryoglobulinemia. HCV polymerase chain reaction revealed genotype 1b with a viral load of 1,314,392 IU/mL.

Over the following days, the patient's renal function deteriorated, with serum creatinine peaking at 5.1 mg/dL. Hemodialysis was started, and renal biopsy revealed typical findings of cryoglobulinemic glomerulonephritis (Figure 1). Transjugular liver biopsy showed grade 1–2 inflammation and stage 2–3 fibrosis (Figure 2). High-dose intravenous steroids were started. The patient was treated with weekly rituximab infusions, plasmapharesis on alternating days, and a 6-week course of prednisone. Renal function tests and RF and complement levels improved, but low levels of cryoglobulins persisted.

Assuming that the cryoglobulinemia was triggered by recurrent HCV infection, urgent retreatment of HCV was pursued. Analysis for HCV resistance-associated variants (RAVs) revealed 3 *NS5A* resistance mutations (A92E, L31M, and Q54H), suggesting ledipasvir resistance as the relapse mechanism. No *NS3/4A* RAVs were identified. Therefore, the patient was treated with a 24-week course of simeprevir, sofosbuvir, and ribavirin. The virus cleared within 8 weeks, and the patient achieved sustained virological response (SVR). Cryoglobulinemia resolved and renal function returned to baseline without further immunosuppression. Repeat renal biopsy revealed very low disease activity with healing lesions (Figure 3).

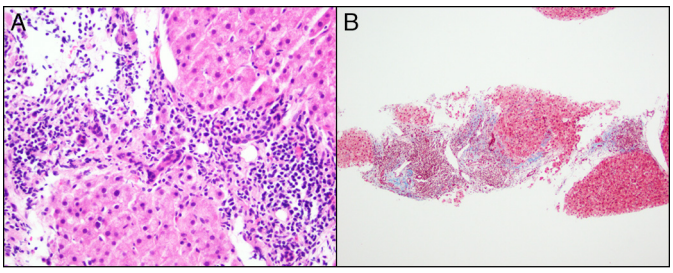

Figure 2. (A) H&E and (B) trichrome stains demonstrating chronic HCV hepatitis with mild to moderate interface activity and focal bridging fibrosis (grade 1-2, stage 2-3).

DISCUSSION

DAA therapies have made treatment of HCV genotype 1 infection very straightforward, with SVR rates reaching 97% in treatment-naïve patients.[2,3] For our patient, we chose a 12-week course of ledipasvir and sofosbuvir, a first-line regimen for treatment-naïve, genotype 1b patients.[4]

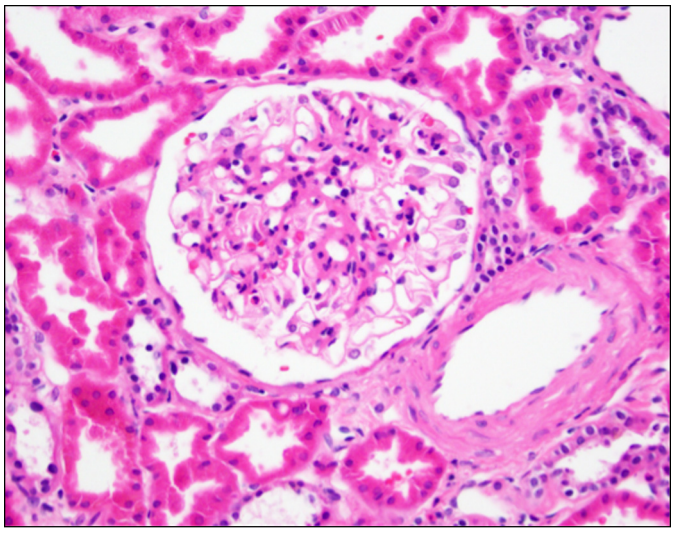

Figure 3. Follow-up renal biopsy with H&E showing a representative glomerulus that demonstrates significantly fewer inflammatory cells and thus improvement of disease activity.

Our patient is among a minority of HCV cases in whom viral relapse occurs after achieving end-of-treatment response with DAAs.[5,6] This was unexpected because he was treatment-naïve and compliant with therapy. Furthermore, his liver biopsy demonstrated only stage 2–3 fibrosis, suggesting that the pretreatment fibroscan revealing cirrhosis likely represented hepatic inflammation, a known confounder of elastography. Molecular analysis demonstrated 3 RAVs in the *NS5A* gene (A92E, L31M, and Q54H), which have been previously described. Generally, the frequency of RAVs in genotype 1b is low compared to genotype 1a.[7] Most genotype 1b RAVs are detected in the *NS5A* region, with L31M being a common culprit.[8] The constellation of RAVs in our patient predicted similar resistance problems with other *NS5A* inhibitors, such as ombitasvir and daclatasvir. In conjunction with the absence *NS3/4A* RAVs, these data provided the rationale for retreatment with sofosbuvir and simeprevir (an *NS3/4A* inhibitor).[7,9] Ribavirin was added and treatment duration was extended to 24 weeks to maximize viral clearance.[10] This regimen ultimately led to successful eradication of the virus.

Virological relapse presenting with de novo cryoglobulinemic vasculitis is an unusual feature of our case. Type II cryoglobulinemia is typically associated with chronic HCV, representing its most dramatic extrahepatic manifestation. It is characterized by inflammation of small and medium-sized vessels secondary to immune complex deposition (containing RF, IgG, HCV RNA, and complement) on endothelial surfaces.[11] Cryoglobulins are classified into three types: type I (monoclonal IgG only), type II (monoclonal IgM, RF, and polyclonal IgG), and type III (polyclonal IgM, RF, and polyclonal IgG).[11,12] Types II and III are mixed cryoglobulins. Disease manifestations range from palpable purpura, arthralgias, and weakness to severe renal and neurological injury.[12] Renal disease can manifest as rapidly progressive glomerulonephritis and portends a poor prognosis. Pathological findings include mesangial cell proliferation, monocytic infiltration, double-contour membranes, and immune-complex deposits.[11] Treatment of HCV-associated mixed cryoglobulinemia includes immunosuppression with rituximab, steroids, and plasmapharesis, as well as antiviral therapy in chronic cases.[13] Serum cryoglobulin concentrations notably do not correlate with disease severity or treatment response.[11]

Treatment of our patient's vasculitis required immunosuppression and plasmapheresis. Rituximab was administered in weekly infusions of 375 mg/m^2 for 4 weeks, with 2 additional doses on days 49 and 77.[14] Intravenous glucocorticoids were administered for 3 days, followed by oral prednisone with a rapid taper.[15] We also used plasmapheresis, which is typically reserved for life-threatening complications including renal disease requiring hemodialysis, respiratory failure, alveolar hemorrhage, hyperviscosity syndromes, and refractory cutaneous vasculitis.[16]

Relapse of cryoglobulinemic vasculitis has been reported in HCV patients despite successful treatment and SVR. These episodes are usually short-lived and may be triggered by underlying immunological abnormalities, such as B-cell lymphoproliferative diseases.[17]

This case demonstrates new-onset cryoglobulinemic vasculitis as a hallmark of virological relapse, in the absence of prior history of vasculitis. Furthermore, it serves as a reminder that HCV may relapse after DAA therapy and that identification of RAVs provides critical guidance when choosing alternative regimens.

DISCLOSURES

Author contributions: MQ Khan reviewed the literature, wrote the manuscript, critically revised the manuscript, and is the article guarantor. AD Moreno reviewed the literature and wrote and edited the manuscript. N. Joseph acquired the imaging, created the figures, and edited the manuscript. G. Kim and CJ Fimmel critically revised the manuscript for intellectual content and supervised the process.

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