A Rare Case of Hepatitis C-Associated Cryoglobulinemic Duodenal Vasculitis

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ABSTRACT
Intestinal involvement of cryoglobulinemia is an uncommon manifestation and marker of severe vasculitis. We describe the case of a woman admitted to our service for management of acute renal failure and progressive gastrointestinal symptoms after initiating hepatitis C virus treatment with ribavirin and sofosbuvir 4 weeks prior. With an undetectable hepatitis C viral load and persistent symptoms despite hepatitis C virus therapy cessation, an upper endoscopy revealed duodenal sloughing, erythema, and bleeding, sparking suspicion for recurrence of cryoglobulinemic vasculitis.

INTRODUCTION
Persistent cryoglobulinemia has been identified with a limited systemic course in the setting of successful and sustained hepatitis C (HCV) treatment. There are limited reports describing intestinal involvement of vasculitis in this setting, a rare marker of severe disease and a diagnosis to be considered in the setting of persistent gastrointestinal (GI) symptoms in patients with a history of HCV. Treatment response to corticosteroids, rituximab, and plasmapheresis has not been previously detailed.

CASE REPORT
A 65-year-old, noncirrhotic, Hispanic woman with HCV genotype 2 (prior null responder to interferon), with known cryoglobulinemic lower extremity vasculitis maintained on mycophenolate mofetil (MMF), was started on sofosbuvir and ribavirin. HCV RNA viral load decreased from 5,453,939 IU/mL to <15 IU/mL after 2 weeks of treatment and was undetectable after 4 weeks. Soon after initiation, she developed severe anemia managed by ribavirin dose reduction and MMF discontinuation and subsequently developed 2 weeks of abdominal pain, vomiting, and diarrhea and presented to our service.

Physical examination revealed anicteric sclera, diffuse tenderness diffusely throughout abdomen without rebound tenderness or guarding, and hyperpigmented lesions confined to the distal lower extremities consistent with...
cryoglobulinemic skin changes (Figure 1). Her abdominal pain was out of proportion to tenderness found on examination. Ribavirin was discontinued upon admission, followed by sofosbuvir, yet symptoms persisted.

An upper endoscopy revealed diffuse duodenal mucosal sloughing with active oozing and underlying dusky pigmented lesions, suspicious for vasculitis (Figure 2). Pathology showed fibro-hemorrhagic material with acute inflammation and fragments of superficial epithelium, with acute inflammation within the lamina propria and markedly congested capillaries with eosinophilic material suggestive of fibrin thrombi. A recurrence of cryoglobulinemia was suspected, in the setting of low complement levels, elevated rheumatoid factor, and absence of antinuclear and antineutrophil cytoplasmic antibodies (Table 1).

Despite fluid resuscitation, she also developed acute kidney injury with a peak creatinine of 2.77 mg/dL, from a baseline of 1.1 mg/dL. Urine electrolytes, urinalysis with proteinuria, and an unremarkable renal ultrasound suggested an intrinsic cause. A confirmatory renal biopsy revealed glomeruli with proliferative features and intercapillary thrombi, basement membranes with focal and segmental double contouring with swollen endothelial cells, and electron dense material in the capillary lumina on electron microscopy (Figure 3). These findings led to the diagnosis of membranous proliferative glomerulonephritis, consistent with HCV-associated cryoglobulinemia.

After receiving high-dose glucocorticoids, the first dose of rituximab, and plasmapheresis, her symptoms rapidly improved, as did renal function. The patient was seen in the outpatient setting with resolution of her symptoms and improvement of renal function; however, a repeat upper endoscopy to confirm mucosal healing could not be performed prior to her return to her home country.

**DISCUSSION**

Few studies have identified cases of cryoglobulinemia in the setting of successful and sustained HCV treatment; however, symptoms are generally confined to mild, cutaneous vasculitis. Retrospective observational studies by Levine et al and Landau et al identified cases of persistent cryoglobulinemia in the setting of successful and sustained HCV treatment, despite prior evidence of correlation between antiviral and vasculitis response in this disease process. However, distinct from our case, symptoms had involved a limited course of purpura and arthralgia.1-3 Intestinal involvement is an uncommonly reported manifestation that may be a marker for increased severity, manifesting in the literature with abdominal pain, and, commonly, perforation.

GI involvement is a rare occurrence, first reported in a case linking intestinal vasculitis to cryoglobulinemia in 1974 and further examined through retrospective review of 163 patients with HCV-associated systemic vasculitis by Terrier et al in 2010. The prevalence is less than 8%, and the presence of intestinal vasculitis is associated with

| Laboratory Parameter | Value | Reference Range |
|----------------------|-------|-----------------|
| Rheumatoid factor, IU/mL | 65 | <14 |
| Complement C3, mg/dL | 54 | 90-180 |
| Complement C4, mg/dL | <4.8 | 10-40 |
| Cryoglobulin | None detected | None detected |
| C-reactive protein, mg/dL | 5.1 | 0.0-0.5 |
| ESR, mm/hr | 31 | 0-20 |
| IgG, mg/dL | 333 | 700-1,600 |
| IgM, mg/dL | 152 | 40-230 |
| ANA | Negative | Negative |
| ANCA | Negative | Negative |

ANA, antinuclear antibodies; ANCA, antineutrophil cytoplasmic antibodies; ESR, erythrocyte sedimentation rate.
increased severity of disease. Abdominal pain was always present at initial presentation, and although 66% of reviewed cases presented with surgical abdomen and/or intestinal bleeding, GI vasculitis was not shown to have a poorer overall survival. Activation of complement and neutrophils in response to immunoglobulin deposition in the capillary lumens cause endothelial damage and fibrin formation, eventually causing ischemia and, potentially, infarction or perforation. 

Mixed cryoglobulinemia typically contains immune complexes containing monoclonal immunoglobulin M rheumatoid factor directed against a polyclonal immunoglobulin G, triggered by the virus itself; however, patients with anti-HCV antibodies with undetectable levels of HCV RNA may still have immune complexes and clinical features of vasculitis. Approximately 30%-40% of patients with Type II cryoglobulinemia do not have detectable circulating cryoglobulins, while hypocomplementemia, presence of rheumatoid factor, and negative antinuclear and antineutrophil cytoplasmic antibodies are typical laboratory features at diagnosis, consistent with our findings. The serum complement pattern does not correlate well with clinical activity. C4 levels may remain persistently low despite normalization of renal function and symptom resolution in patients with cryoglobulinemic glomerulonephritis and in patients with successful HCV treatment with clearance of cryoglobulins.

Rituximab and intravenous glucocorticoids were administered given an undetectable viral load and presence of membranous proliferative glomerulonephritis, followed by plasmapheresis. Rituximab is a monoclonal antibody targeting CD-20+ proliferating B-cell clones that result in a decrease of a rheumatoid factor-producing B-cell subset. Combination with glucocorticoids has been shown to decrease disease activity. With the addition of rituximab to peginterferon alfa and ribavirin, complete response rates in patients with cryoglobulinemic vasculitis have significantly increased as well.

Premature discontinuation of MMF during HCV treatment was likely the cause of vasculitis recurrence due to resolution of vasculitis, whereas on MMF, recurrence immediately upon discontinuation, and resolution again once immunosuppressive therapy was begun. However, we cannot explain the increased severity of vasculitis with discontinuation of MMF as the patient had not presented with GI tract involvement or membranous proliferative glomerulonephritis when MMF was begun that we are
aware of. Exacerbations of vasculitis have also been reported during HCV treatment, attributed to peginterferon; however, HCV treatment in our case was interferon free.\textsuperscript{18,19}

Our findings emphasize consideration of intestinal vasculitis as a cause of persistent GI symptoms in patients with a history of hepatitis C, including those with successful eradication of HCV undergoing treatment, and demonstrate an immediate improvement in GI symptoms and renal function with short-term corticosteroids, rituximab, and plasmapheresis. Our case adds to the existing small body of literature on intestinal cryoglobulinemic vasculitis and highlights the pathophysiology of this complex, viral-mediated immunologic mechanism and its management.

DISCLOSURES

Author Contributions: S. Berera, A. Gomez, and K. Dholaria performed the literature review and wrote the manuscript. L. R. Arosemena, KR Bhamidimarri, and MA Ladino-Avellaneda revised and reviewed the manuscript. L. Barisoni provided the pathology slides and analysis. KR Bhamidimarri is the article guarantor.

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This article has been corrected. In the author list, an incorrect middle initial “R.” was removed from the name of author Shivali Berera.