Hepatitis C Virus-Associated Aortitis Caused by Type I Cryoglobulins

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ABSTRACT
Chronic hepatitis C virus infection (HCV) can present with cryoglobulinemic vasculitis, which is primarily associated with type II/III cryoglobulins. Type I cryoglobulins are usually seen in lymphoproliferative disease, and large vessel involvement with this type of vasculitis is rare. A 70-year-old man with chronic HCV presented with abdominal pain, leukocytosis, and rash. Computed tomography angiography showed thickening of the abdominal aorta consistent with large-vessel vasculitis. He was found to have type I cryoglobulinemia and was treated with corticosteroids and ledipasvir/sofosbuvir with rapid resolution of his aortitis. This case emphasizes the need to recognize HCV as a potential etiology of large-vessel vasculitis.

INTRODUCTION
Chronic hepatitis C virus (HCV) infection can present with many extrahepatic manifestations, the most common of which is cryoglobulinemia. Cryoglobulinemic vasculitis is characterized by the cold precipitation of serum cryoglobulins on endothelial surfaces, which elicits vascular inflammation through mechanisms that are not completely understood. HCV is primarily associated with type II and type III cryoglobulins, which are mixtures of monoclonal immunoglobulins IgM and polyclonal IgG and polyclonal IgM and IgG, respectively.1,2 In rare instances, type I cryoglobulins (monoclonal IgG or IgM, less commonly IgA) have also been seen with HCV, although type I cryoglobulinemia is classically described in lymphoproliferative disorders.3 HCV-associated cryoglobulinemic vasculitis primarily affects small and medium-sized vessels of the skin, kidneys, and peripheral nerves.1 Involvement of large vessels, such as the aorta, is unusual and rarely described in the literature.

CASE REPORT
A 70-year-old white man with a history of chronic, non-cirrhotic HCV (genotype 1a, treatment naïve) presented with a 1-week history of right lower quadrant abdominal pain and a new, erythematous rash on his trunk and bilateral lower extremities. Laboratory studies included a leukocytosis of 14 K/μL, with normal renal function, liver function, and coagulation tests. Computed tomography angiography showed diffuse wall thickening of the distal abdominal aorta and common iliac vessels without evidence of an aortic aneurysm or aortic dissection (Figure 1). These findings were suspicious for focal, large-vessel vasculitis, and the patient was admitted.

Additional workup revealed an elevated erythrocyte sedimentation rate of 34 mm/hr and C-reactive protein 8.7 mg/dL. Human immunodeficiency virus, rapid plasma reagin, and treponemal antibody testing were negative. The patient had a positive antinuclear antibody test (titer >1:1,280, nucleolar pattern), but p- and c-anti-neutrophil cytoplasmic antibody, IgG4 level, double-stranded DNA antibodies, anti-Smith antibodies, anti-ribonucleoprotein antibodies, and complement levels (C3/C4) were negative. HCV viral load was elevated at 183,424 IU/mL, and serum
was positive for type I cryoglobulins composed of IgG λ monoclonal proteins. Serum protein electrophoresis was unremarkable.

Punch biopsy of the patient’s rash showed papillary dermal edema and a mild superficial perivascular inflammatory infiltrate, consistent with a non-specific, superficial perivascular dermatitis (Figure 2). On hospital day 7, he was started on ledipasvir/sofosbuvir 90–400 mg daily as well as prednisone 40 mg daily for HCV-induced cryoglobulinemic vasculitis involving the small vessels of the skin and the large vessel of the aorta. The patient completed a 12-week course of ledipasvir/sofosbuvir and subsequently achieved a sustained virologic response. Repeat magnetic resonance angiography 4 months later showed complete resolution of the thickening in the abdominal aorta and common iliac arteries (Figure 3). Repeat cryoglobulin level was negative 2 months after starting ledipasvir/sofosbuvir, and the patient was able to be tapered off steroids within 7 months.

**DISCUSSION**

The prevalence of cryoglobulinemia in HCV varies from 10–54% of infected individuals and is more common in women, older patients, and those with longer durations of infection.4-7 Clinical symptoms include palpable purpura, arthralgias, Raynaud’s phenomenon, peripheral neuropathy, and renal impairment.8 HCV-associated cryoglobulinemic vasculitis typically affects small and medium-sized vessels, while involvement of larger vessels, such as the aorta, is rarely reported. Rather, aortitis is classically caused by bacterial infections such as *Salmonella*, *Staphylococcus*, or syphilis, or it is secondary to inflammatory conditions including giant cell arteritis, Takayasu arteritis, rheumatoid arthritis, and systemic lupus erythematosus.9,10 While the reasons for these differences in vessel size are not completely known, a possible explanation is that cryoglobulinemic vasculitis is frequently mediated by immune complex formation, which is more likely to precipitate in smaller vessels.11 Conversely, giant cell arteritis and Takayasu arteritis involve large-vessel infiltration of T-cells, macrophages, and monocytes.2

Although infrequently seen, a few case series and case reports have established an association between cryoglobulinemia
and aortic abnormalities in non-HCV-infected patients.\textsuperscript{13,14} However, aortitis secondary to HCV-associated cryoglobulinemia is not well defined. Fukunaga et al. described a case of an elderly man with known HCV-related cryoglobulinemia who presented with an aortic dissection and histopathology that showed deposition of IgG within the aortic wall.\textsuperscript{15} The man was treated with steroids, underwent emergent reconstructive surgery, and ultimately survived. However, the authors did not comment on definitive treatment of his underlying HCV. Our case is unique because our patient’s aortitis resolved with oral antiviral therapy in addition to corticosteroids.

As previously mentioned, HCV-related cryoglobulinemic vasculitis is most commonly associated with type II and III cryoglobulins, whereas type I cryoglobulinemia is typically seen in lymphoproliferative disorders.\textsuperscript{2,7} However, type I cryoglobulins have also occasionally been reported in patients with HCV. A case series by Trejo et al. reported that, out of 90 patients with type-able cryoglobulinemia, 33 patients had type I cryoglobulins, 83\% of which also had concurrent HCV infection.\textsuperscript{3} Our case highlights a unique presentation of HCV-related cryoglobulinemic vasculitis associated with type I cryoglobulins. Lymphoproliferative disorders were ruled out via negative serum electrophoreses and the absence of lymphadenopathy on computed tomography imaging. HCV as the etiology of this case highlights a unique presentation of HCV-related cryoglobulinemia in a patient who had type I cryoglobulins. 83\% of which also had concurrent HCV infection. Our case was also supported by the resolution of vascular inflammation and clearance of serum cryoglobulins with antiviral therapy.

In accordance with guidelines, patients with HCV-associated cryoglobulinemic vasculitis should receive treatment for HCV, with direct-acting antivirals being the preferred agents.\textsuperscript{18,19} While these guidelines were based on studies of vasculitis in small and medium-sized vessels, the present case suggests that these recommendations should be extrapolated to include large-vessel vasculitis. Corticosteroids are often used as an additive therapy to help mitigate vasculitic flares.\textsuperscript{20} Our patient was treated with steroids and antiviral therapy, achieving both sustained virologic response and resolution of vasculitis.

This case highlights a rare presentation of HCV-associated aortitis caused by type I cryoglobulins that ultimately resolved with antiviral therapy. The rapid improvement of vasculitis, cryoglobulinemia, and HCV infection following initiation of sofosbuvir/ledipasvir emphasizes the need to search for a viral etiology in similar cases and to promptly begin potentially life-saving therapy.

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DISCLOSURES

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