ACG CASE REPORTS JOURNAL

CASE REPORT | LIVER

# Hepatitis C Virus-Associated Aortitis Caused by Type I Cryoglobulins

Adrienne Lenhart, MD[1], Alireza Meighani, MD[1], Mona Hassan, MD[2], and Stuart Gordon,MD[2]

[1]*Department of Internal Medicine, Henry Ford Hospital, Detroit, MI*
[2]*Division of Gastroenterology and Hepatology, Henry Ford Hospital, Detroit, MI*

## 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/$\mu$L, 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

*ACG Case Rep J* 2017;4:e114. doi:10.14309/crj.2017.114. Published online: October 25, 2017.

**Correspondence:** Adrienne Lenhart, Department of Internal Medicine, Henry Ford Hospital, 2799 W Grand Blvd, Detroit, MI 48202 (alenhar2@hfhs.org).

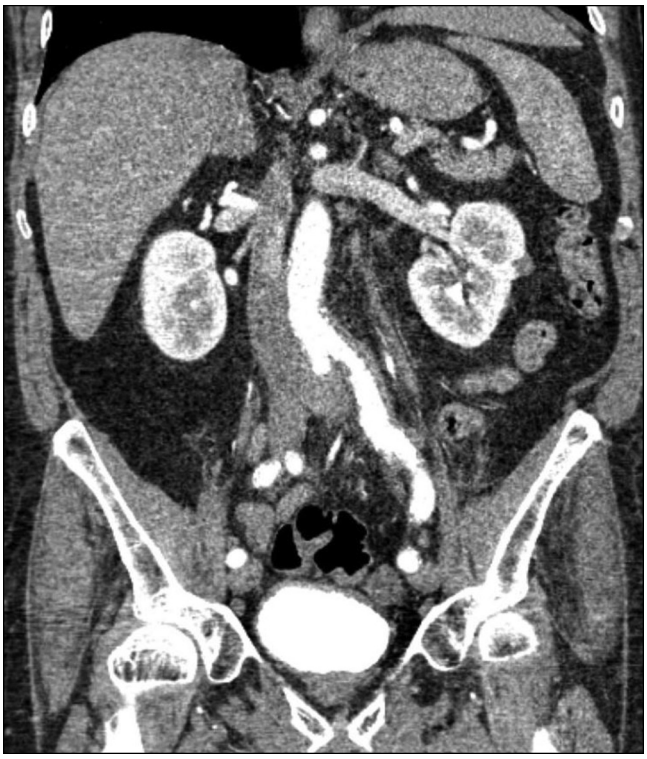

**Figure 1.** Computed tomography angiography of the abdomen showing diffuse thickening of the walls of the abdominal aorta and common iliac vessels.

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

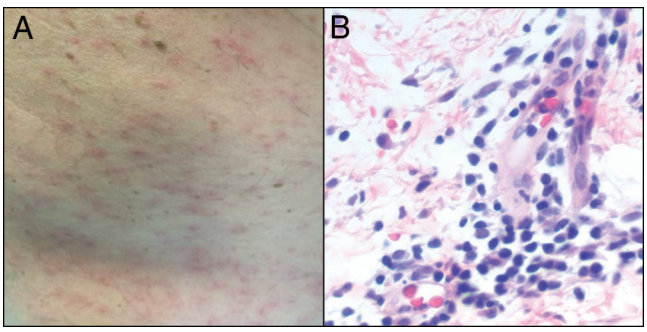


**Figure 2.** (A) Blanching, erythematous macules, and papules on the patient's upper back. (B) Histopathology showing papillary dermal edema and a superficial perivascular inflammatory infiltrate.

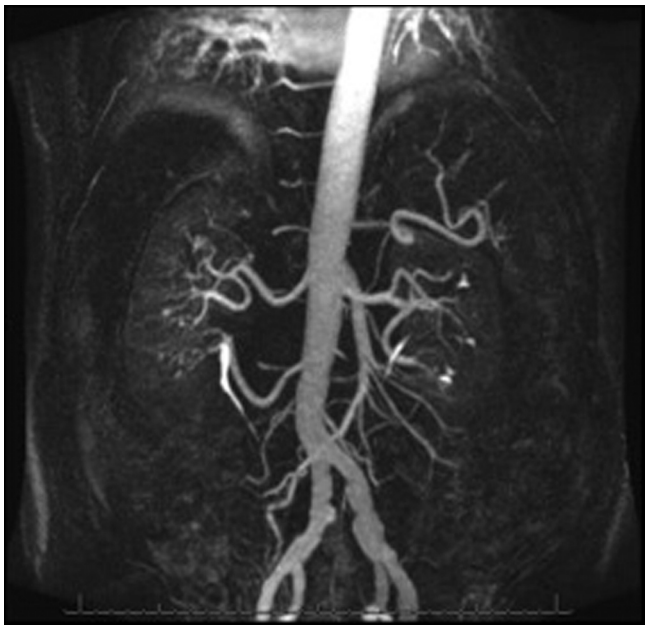

**Figure 3.** Magnetic resonance angiography of the abdomen showing resolution of aortitis in the distal aorta and proximal iliac vessels.

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.[12]

Although infrequently seen, a few case series and case reports have established an association between cryoglobulinemia

and aortic abnormalities in non–HCV-infected patients.[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.[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.[16,17] 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.[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 patient's type I cryoglobulinemia 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.[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.[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.

## DISCLOSURES

Author contributions: A. Lenhart wrote the manuscript and is the article guarantor. A. Meighani and M. Hassan wrote and edited the manuscript. S. Gordon edited the manuscript.

Financial disclosure: None to report.

Informed consent was obtained for this case report.

Received April 13, 2017; Accepted September 13, 2017

## REFERENCES


1. Charles ED, Dustin LB. Hepatitis C virus-induced cryoglobulinemia. *Kidney Int*. 2009;76(8):818–24.
2. Brouet JC, Clauvel JP, Danon F, et al. Biologic and clinical significance of cryoglobulins: A report of 86 cases. *Am J Med*. 1974;57:775–88.
3. Trejo O, Ramos-Casals M, García-Carrasco M, et al. Cryoglobulinemia: Study of etiologic factors and clinical and immunologic features in 443 patients from a single center. *Medicine*. 2001;80(4):252–62.
4. Lunel F, Musset L, Cacoub P, et al. Cryoglobulinemia in chronic liver diseases: Role of hepatitis C virus and liver damage. *Gastroenterology*. 1994;106(5):1291–300.
5. Adinolfi LE, Utili R, Attanasio V, et al. Epidemiology, clinical spectrum and prognostic value of mixed cryoglobulinaemia in hepatitis C virus patients: A prospective study. *Ital J Gastroenterol*. 1996;28(1):1–9.
6. Wong VS, Egner W, Elsey T, Brown D, Alexander GJ. Incidence, character and clinical relevance of mixed cryoglobulinaemia in patients with chronic hepatitis C virus infection. *Clin Exp Immunol*. 1996;104(1):25–31.
7. Cicardi M, Cesana B, Del Ninno E, et al. Prevalence and risk factors for the presence of serum cryoglobulins in patients with chronic hepatitis C. *J Viral Hepat*. 2000;7(2):138–43.
8. Dammacco F, Racanelli V, Russi S, Sansonno D. The expanding spectrum of HCV-related cryoglobulinemic vasculitis: A narrative review. *Clin Exp Med*. 2016;16:233–42.
9. Rojo-Leyva F, Ratliff NB, Cosgrove DM 3rd, Hoffman GS. Study of 52 patients with idopathic aortitis from a cohort of 1,204 surgical cases. *Arthritis Rheum*. 2000;43:901–7.
10. Pacini D, Leone O, Turci S, et al. Incidence, etiology, histologic findings, and course of thoracic inflammatory aortopathies. *Ann Thorac Surg*. 2008;86(5):1518–23.
11. Cacoub P, Comarmond C, Domont F, Savey L, Saadoun D. Cryoglobulinemia vasculitis. *Am J Med*. 2015;128(9):950–5.
12. Weyand CM, Goronzy JJ. Medium- and large vessel vasculitis. *N Engl J Med*. 2003;349(2):160–9.
13. Au WY, Kwok JS, Chu KM, Ma ES. Life-threatening cryoglobulinemia in HCV-negative Southern Chinese and a novel association with structural aortic abnormalities. *Ann Hematol*. 2005;84(2):95–8.
14. Dabala A, Musso L, Oreste PL, et al. Antiapolipoprotein B cryoglobulinemia associated with normal plasma lipids and severe atherosclerosis. *Appl Pathol*. 1986;4(4):260–9.
15. Fukunaga N, Fujiwara H, Nasu M, Okada Y. Aortic dissection caused by aortitis associated with hepatitis C virus-related cryoglobulinemia. *J Thorac Cardiovasc Surg*. 2010;140(5):e81–2.
16. Néel A, Perrin F, Decaux O, et al. Long-term outcome of monoclonal (type 1) cryoglobulinemia. *Am J Hematol*. 2014;89(2):156–61.
17. Terrier B, Karras A, Kahn JE, et al. The spectrum of type I cryoglobulinemia vasculitis: New insights based on 64 cases. *Medicine*. 2013;92(2):61–8.
18. AASLD/IDSA HCV Guidance Panel. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. *Hepatology*. 2015;62(3):932–54.
19. European Association for Study of Liver. EASL recommendations on treatment of hepatitic C 2015. *J Hepatol*. 2015;63(1):199–236.
20. Dammacco F, Sansonno D, Han JH, et al. Natural interferon-alpha versus its combination with 6-methyl-prednisolone in the therapy of type II mixed cryoglobulinemia: A long-term, randomized, controlled study. *Blood*. 1994;84(10):3336–43.