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CASE REPORT

Myopericarditis in a patient with hepatitis C and cryoglobulinemic renal disease

Mohamoud A. Ali[1], Waqas Z. Kayani[2], Bradley M. Linzie[3], Gopal V. Punjabi[4] & James B. Wetmore[5,6]

[1]Department of Medicine, Hennepin County Medical Center, Minneapolis, Minnesota, USA
[2]Department of Family & Community Medicine, UND School of Medicine and Health Sciences, Minot, North Dakota, USA
[3]Department of Pathology, Hennepin County Medical Center, Minneapolis, Minnesota, USA
[4]Department of Radiology, Hennepin County Medical Center, Minneapolis, Minnesota, USA
[5]Division of Nephrology, Hennepin County Medical Center, Minneapolis, Minnesota, USA
[6]Chronic Disease Research Group, Minneapolis, Minnesota, USA

Correspondence
Mohamoud A. Ali, Department of Medicine, Hennepin County Medical Center, Medicine Education Program, G5.125, 701 Park Ave., Minneapolis, 55415 MN, USA. Tel: 985-260-0064; Fax: 612-904-4577;
E-mail: mohamoudali@me.com

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Key Clinical Message

Although cryoglobulinemia is a well-appreciated complication of hepatitis C (HC), myopericarditis with resulting pericardial effusion is extremely rare, especially in the absence of a liver transplant. In patients with HC, pericardial effusion with impending tamponade can be a florid and potentially life-threatening manifestation of multiorgan cryoglobulinemic disease.

Keywords

Cryoglobulinemia, hepatitis C, membranoproliferative glomerulonephritis, myocarditis, pericarditis, vasculitis.

Introduction

Chronic hepatitis C (HC) is a major public health concern, with the World Health Organization reporting that approximately 3% of the world's population suffers from the disease [1]. A well-established extrahepatic complication of HC infection is mixed cryoglobulinemic vasculitis type II, a serious disorder in which cryoglobulins containing monoclonal immunoglobulin type M (IgM) with rheumatoid factor activity against polyclonal IgG are deposited in various tissues. Indeed, HC likely accounts for >80% of the cases of cryoglobulinemia. Typical clinical manifestations of HC-associated cryoglobulinemic vasculitis include palpable purpura, arthritis, glomerulonephritis, peripheral neuropathy, and many others.

Rarely, however, do affected individuals develop cardiac-related manifestations such as myopericarditis. One study suggested that there were only five reported cases of HC-infected patients with cryoglobulinemia who developed cardiac-related manifestations in all the literature [2]; in each case, the individual was a liver transplant recipient who subsequently developed isolated pericarditis without myocardial involvement. In a more recent study of 165 HC-infected patients who were not liver transplant recipients, only one patient appeared to a have both pericardial effusion and myocardial involvement [3]. It is typically in non-HC-related systemic disorders, such as Sjogren's syndrome, that cardiac involvement such as pericarditis is most commonly encountered [4]. Thus, while there appears to be a link between cryoglobulinemia and cardiac manifestations such as pericarditis in certain clinical settings, there are few distinct reports of HC-associated cryoglobulinemic myopericarditis. In the present report, we describe what we suggest is a rare case of HC-associated mixed cryoglobulinemic vasculitis presenting as myopericarditis in the absence of a previous liver transplant.

Case Presentation

A 45-yr-old male with a known history of HC (genotype 1a) diagnosed approximately 6.5 years prior to admission on routine screening presented to the Hennepin County Medical Center emergency department with 4 days of fever, pleuritic chest pain, and generalized abdominal pain complicated by intractable nausea. The patient denied use of drugs of abuse such as cocaine, heroin, or methamphetamines, or use of immunosuppressants (e.g., cyclophosphamide), antipsychotics (e.g., clozapine or phenothiazines), or mood-altering drugs (lithium or tricyclic antidepressants). On exam, he had a temperature of 38.6°C, blood pressure of 157/85 mmHg, heart rate of 108 bpm, a diffusely tender abdomen, and bilateral lower extremity edema. Laboratory studies revealed a marked troponin elevation (peak 13 g/dL 18 h after presentation) in the setting of diffuse ST-wave elevation in a noncoronary distribution on electrocardiography and a serum creatinine of 6.0 mg/dL. Cardiac evaluation commenced with a two-dimensional transthoracic echocardiography (TTE), which exhibited a small pericardial effusion without ischemic regional wall motion abnormality (Fig. 1A); this prompted follow-up cardiac magnetic resonance imaging that revealed pericardial thickening and enhancement consistent with pericarditis as well as subepicardial foci of delayed enhancement suggestive of myocarditis (Fig. 1B). Simultaneous renal evaluation and management initially consisted of an overnight bolus of intravenous fluid; as the creatinine did not improve, a urinalysis was performed, which revealed blood and protein.

In an attempt to unify the cardiac and renal findings, a more extensive serologic workup was commenced. This demonstrated a positive antinuclear antibody (indirect immunofluorescence assay titer 1:320), positive antineutrophil cytoplasmic antibodies (indirect immunofluorescence titer 1:20), positive anti-SSA and anti-RNP (both via solid phase assay), and elevated rheumatoid factor (105 IU/mL). However, serum IgA, IgG, IgM, anti-double-stranded DNA, anti-Smith antibodies, and serum cryoglobulins were all either within normal limits or undetectable. HIV antigen/antibody testing was also negative. Because an autoimmune process was strongly suspected, and because of the possibility of a false-negative cryoglobulin assay, the treatment team performed a renal biopsy, which demonstrated glomeruli with diffuse endocapillary proliferation and PAS-positive hyaline thrombi (Fig. 2A). Arterioles also contained PAS-positive hyaline thrombi and fibrin thrombi with endothelial swelling. Immunofluorescence identified hyaline thrombi and mesangial deposits as immune complexes containing IgM and C3 (not shown). Electron microscopy showed curvilinear substructure to the electron-dense intraluminal and mesangial deposits characteristic of cryoglobulinemic glomerulonephritis (Fig. 2B). The interstitium demonstrated mild patchy fibrosis and mild edema, but the tubules appeared normal. Intermediate-size arteries were unremarkable. Lupus glomerulonephritis was excluded by the lack of IgG, IgA, and C1q on immunofluorescence study. These findings were considered consistent with cryoglobulinemic glomerulonephritis, a form of membranoproliferative glomerulonephritis (MPGN). At that time, the patient was thought to have viral pericarditis; after failing therapy with full-dose aspirin and colchicine, he was placed on systemic glucocorticoids, improved clinically, and was discharged.

The patient was then lost to follow-up, returning 3 months later with similar symptoms of abdominal pain, pleuritic chest pain, and new-onset dyspnea in the setting of a milder troponin elevation (0.05 μL). Glomerular filtration rate was substantially lower than before at 15 mL/min/1.73 m^2 (based on Modified Diet in Renal Disease equation [5]) accompanied by recurrent abnormalities of the urine sediment (protein 100 mg/dL, white blood cells

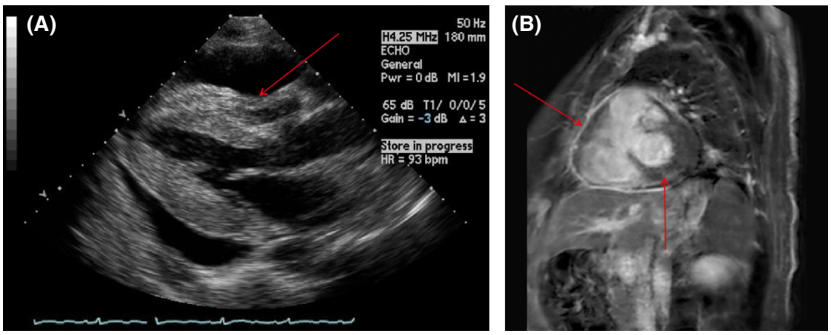

Figure 1. (A) Presence of a large, circumferential pericardial effusion with evidence for early diastolic collapse (arrow) of the right ventricle, consistent with impending tamponade physiology. (B) Phase sensitive inversion recovery sequence obtained 8 min after infusion of intravenous gadolinium. Short-axis plane showed diffuse pericardial thickening and punctate subepicardial foci of delayed enhancement in the inferolateral wall.

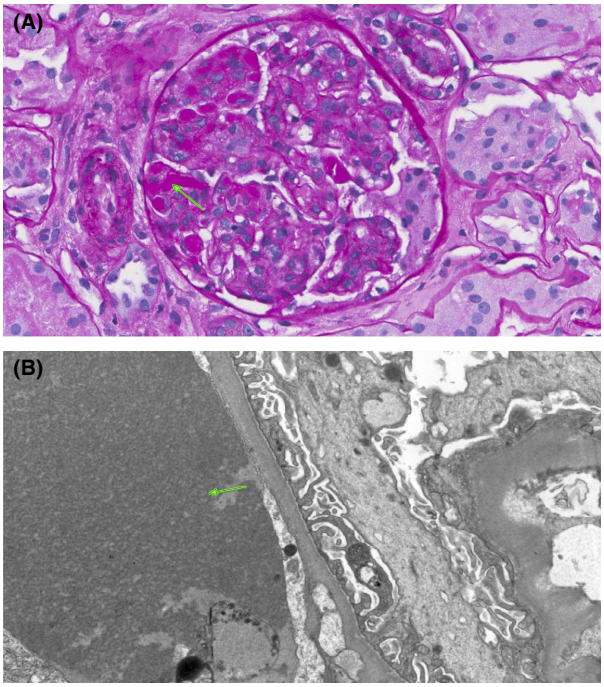

Figure 2. (A) Glomeruli demonstrated diffuse endocapillary proliferation and PAS-positive hyaline thrombi. (B) Electron microscopy showed curvilinear substructure to the electron-dense intraluminal and mesangial deposits characteristic of cryoglobulinemic glomerulonephritis.

and red blood cells 6–20 cells per high power field). Repeat TTE revealed the new finding of a large, circumferential pericardial effusion with evidence for early diastolic collapse of the right ventricle, consistent with impending tamponade physiology. He underwent a therapeutic and diagnostic pericardiocentesis; gram stain and culture were negative, and no malignant cells were observed. He was then treated with pulse steroids.

Unfortunately, his course was further complicated by a syndrome of rapidly progressive glomerulonephritis, volume overload, persistent abdominal pain, and painful palpable purpuric skin lesions of the lower extremities. The worsening of his symptoms prompted escalation of therapy with rituximab, plasmapheresis, and the initiation of intermittent hemodialysis. After receiving six plasmapheresis treatments, his symptoms improved substantially, but he remained dialysis dependent. Upon discharge, the patient was referred to the hepatology clinic for consideration of treatment with novel direct-acting antivirals.

Discussion

Cryoglobulinemic vasculitis, as demonstrated by the pattern of diffuse ST-wave, changes in a non-coronary-artery distribution, a large, hemodynamically significant pericardial effusion on echocardiography, and intact left ventricular systolic function. The presentation, with the large effusion and marked acute kidney injury, was striking. While treatment with rituximab and plasmapheresis improved many of symptoms, he became dialysis dependent. Although we cannot be certain that the patient's myocarditis improved, the patient's overall clinical improvement, the reduction in the size of the pericardial effusion, and the decrease in the circulating levels of the cardiac biomarkers following therapy make it likely that this was case; reassessment of the myocarditis using a gadolinium-enhanced MRI scan was judged to confer risk disproportionate to any potential benefit in a patient with severe renal insufficiency.

The occurrence of cardiac disorders associated with HC-induced cryoglobulinemic vasculitis appears to be uncommon, with only a handful of case reports describing this phenomenon. Most of these reports appear to be confined to patients who were liver transplant recipients [2], and of these, none appear to have demonstrated myocarditis specifically. While myopericarditis has been reported in Sjogren's disease-associated cryoglobulinemia, this was in the absence of HC [4]. Only one HC-infected patient, as described below, has been reported to have had a pericardial effusion in the absence of a liver transplant and may have had myocarditis; this patient, in distinction to ours, appears to have had left ventricular hypokinesis [6]. Thus, our case therefore appears to be one of the first reports of myopericarditis in an HC patient who was not a liver transplant recipient, and perhaps the first in one in which systolic heart function was preserved.

Myopericarditis has rarely been reported in the clinical literature, and because most cases of acute myopericarditis are viral in origin [7], initial treatment was undertaken with full-dose nonsteroidal anti-inflammatory agents and colchicine, a therapy which might have been expected to have had a >90% chance of inducing a response [8]. However, because the patient's symptoms were refractory to first-line therapy, we sought an alternative etiology, the most common of which are mycobacterium tuberculosis (MTB) and autoimmune diseases. As MTB was ruled out, a course of glucocorticoids and rituximab was initiated [6], which resulted in an improvement in patient's pleuritic chest pain, a reduction in diffuse ST-wave elevation, and a decrease in the elevated cardiac biomarkers. While the absence of a myocardial biopsy means that myocarditis cannot be definitively diagnosed, the constellation of findings, response to therapy, and a highly suggestive renal biopsy demonstrating cryoglobulinemic-associated MPGN makes HC-associated cryoglobulinemic

myopericarditis the most likely explanation for the patient's findings.

We considered the possibility that HC virus could directly account for the findings. The HC virus itself has cardiotropic properties, with one study reporting HC-associated pericardial effusion and tamponade in a liver transplant recipient [2]. In that study, a clinically significant pericardial effusion with tamponade physiology was detected by Doppler echocardiography and cardiac magnetic resonance imaging (MRI). While HC viral RNA was present in pericardial fluid, there were no clinical or laboratory abnormalities to suggest the presence of mixed essential cryoglobulinemia, making cryoglobulinemia an unlikely agent in that reported case [2]. In addition, myocardial involvement, as evidenced by either cardiac biomarker elevation or magnetic resonance imaging, was not reported. Thus, direct effects of HC virus (i.e., effects independent of cryoglobulinemia) seem unlikely.

That cryoglobulins were likely to be directly involved in the present patient is suggested by reports that myopericardial disease, specifically, has occurred in patients with cryoglobulinemic vasculitis associated with Sjogren's disease (in the absence of HC coinfection) [9]. However, there appear to be no case reports of myopericarditis associated with primary Sjogren's syndrome in the absence of mixed cryoglobulinemic vasculitis. Myocardial involvement appears to be very rare in HC-related mixed cryoglobulinemic vasculitis: In a retrospective cohort of 165 consecutive patients with HC-related mixed cryoglobulinemic vasculitis, myocardial disease was described in seven patients, of whom only three (<2%) had objective findings on MRI [3]. Only one patient also had a pericardial effusion (without mention of tamponade), but he/she exhibited dilated cardiomyopathy, in contrast to our patient who had preserved left ventricular systolic function.

The mechanism by which cryoglobulins affect the myocardium appears to be via small-vessel vasculitis. In the large case series above [3], none of the four individuals who underwent angiography had obstructive disease, a finding consistent with other reports which suggest that cryoglobulin-related heart disease typically involves the coronary microcirculation and spares the major arteries [10]. While it is uncertain precisely how cryoglobulinemic vasculitis affects the myocardium, the treatment course pursued in the present case suggests that the cryoglobulinemic vasculitis itself, and not the cardiotropic effects of HC virus, was the etiologic agent of myopericarditis. Immunosuppression with anti-CD20 therapy and glucocorticoids, which would be expected to potentially increase viral replication and hepatitis flares [11], was effective in treating this patient.

The present report has some limitations. First, an endomyocardial biopsy was not performed because the evolving clinical scenario strongly implicated myocardial disease, the potential for sampling error (a well-established complexity of endomyocardial biopsy [12]) was substantial, and, in the absence of hemodynamic instability, the procedure was unlikely to yield information that would directly impact therapy. Second, the serum cryoglobulin assay was negative, despite high clinical suspicion. Testing for cryoglobulins is complicated by lack of reference range, standards, and stringency in maintaining testing temperature conditions. The specimen must be maintained between 37°C and 41°C from the time of its procurement until the serum is isolated in the laboratory [13]. If the specimen is exposed to temperatures lower than 37°C at any time before the serum is obtained, the cryoprecipitate may be lost [14]. Thus, the most likely source of a false-negative result, as has been reported in a previous biopsy-proven case [15], is loss of cryoprecipitate during transport and storage. In addition, episodic failure to detect cryoglobulins may reflect fluctuations in cryoglobulin levels, which even at low levels can be associated with severe symptoms in some patients [13]. Finally, the exact pathophysiologic mechanism of the disease process we posit is unknown. Our goal, however, was to raise awareness about an apparently rare clinical entity with potentially life-threatening complications, and to stimulate interest in further study.

In conclusion, this may be only the second reported case of myopericarditis presumed due to HC-associated cryoglobulinemia in the absence of a liver transplant, and the first case, to our knowledge, with preserved left ventricular systolic function. The clinical presentation of the large pericardial effusion and markedly poor renal function is quite unusual. The relationship between the presenting cardiac findings and other clinical manifestations, the renal biopsy findings (which demonstrated cryoglobulinemic vasculitis as the mechanism of injury), and the overall responsiveness to immunosuppressive therapy strongly suggest causality. More work is required to investigate the mechanisms underlying how HC-associated cryoglobulinemia might affect the myopericardium. In the meantime, clinicians should be careful to assess for possible cardiovascular involvement in patients with cryoglobulinemic vasculitis.

Conflicts of Interest

The authors have no conflict of interests to declare.

Authorship

MAA: involved in conception and design of work, data collection, patient interview, drafting article, literature search, data analysis and interpretation. WZK: involved in drafting article, literature search, and data collection. BML: Figure 2A/B image acquisition and pathological slide analysis and interpretation. GVP: helped in Figure 1A/B image acquisition, interpretation and analysis of cardiac MRI and 2D transthoracic echocardiography. JBW: involved in design of work, critical revision of article, final approval of version to be published.

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