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Cryoglobulinemic vasculitis in two patients with infective endocarditis: a case series

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***Abstract*:** Cryoglobulins are circulating immune complexes that precipitate at cool temperatures and can induce a small-vessel vasculitis. While patients with endocarditis are well known to have circulating cryoglobulins, cryoglobulinemic vasculitis is a rare complication of infective endocarditis with infrequent publication of reported cases. We present two cases of methicillin-resistant *Staphylococcus aureus* tricuspid valve infective endocarditis in patients with substance use disorder complicated by cryoglobulinemic cutaneous vasculitis confirmed by skin biopsy, including one patient who developed renal and colonic manifestations of vasculitis. Both patients had symptomatic improvement in their vasculitis with appropriate antimicrobial therapy, including one patient who received a short course of prednisone and another with chronic active hepatitis C that remained untreated. Providers should have a high-index of suspicion for infective endocarditis in patients presenting with new onset cryoglobulinemic vasculitis, particularly if the patients have underlying risk factors for endocarditis.

Keywords: cryoglobulinemia, endocarditis, hepatitis C, vasculitis

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Introduction

Cryoglobulins are circulating immune complexes that precipitate at cool temperatures and can induce a small-vessel vasculitis with associated cutaneous, renal and gastrointestinal manifestations.[1] Cryoglobulinemic vasculitis is most commonly diagnosed in the setting of hepatitis C infection.[1,2] While patients with endocarditis are well known to have circulating cryoglobulins, cryoglobulinemic vasculitis is a rare complication of infective endocarditis.[3] Here we present two cases of cryoglobulinemic vasculitis with cutaneous manifestations diagnosed in the setting of endocarditis.

Case 1

A 40-year-old male was admitted to the hospital in February 2022 following 1 week of chest pain, chills, and fatigue. His past medical history was pertinent for substance use disorder and injection drug use, chronic active hepatitis C, prior methicillin-susceptible *Staphylococcus aureus* (MSSA) tricuspid valve endocarditis in 2016 treated with intravenous antibiotics and tricuspid valve annuloplasty as well as methicillin-resistant *Staphylococcus aureus* (MRSA) tricuspid valve endocarditis in December 2021 diagnosed and treated by another institution with 6 weeks of intravenous vancomycin. On admission laboratory studies were notable for a white blood cell count of 16,740/μL, hemoglobin of 12.8 g/dL, platelets count of 69,000/μL, serum creatinine of 2.07 mg/dL, c-reactive protein (CRP) of 302.5 mg/L and erythrocyte sedimentation rate (ESR) of 62 mm/hr. Admission blood cultures were positive for MRSA (Table 1). Transthoracic echocardiogram (TTE) on hospital day #1 demonstrated a 1.5 cm tricuspid valve vegetation. He was initially treated with intravenous vancomycin; however, on hospital day #2 he developed painful palpable purpura with tense overlying bullae on the bilateral upper and lower extremities (Figure 1) with associated joint pain. Consequently, due to concerns for a possible drug reaction, vancomycin was discontinued and he was started on daptomycin and

Table 1. Pertinent laboratory results for both cases of cryoglobulinemic vasculitis.

Laboratory Test	Case 1	Case 2
White blood cell count	16,740/μL	16,860/μL
Hemoglobin	12.8 g/dL	13.8 g/dL
Platelet count	69,000/μL	1640,000/μL
Serum creatinine	2.07 mg/dL	0.92 mg/dL
C-reactive protein	302.5 mg/L	200.6 mg/L
Erythrocyte sedimentation rate	62 mm/hour	30 mm/hour
Blood culture results	Methicillin-resistant *Staphylococcus aureus*	Methicillin-resistant *Staphylococcus aureus*
C3	50 mg/dL	97 mg/dL
C4	10 mg/dL	4 mg/dL
Quantitative cryoglobulin immunoglobulin A	46 mg/dL	9 mg/dL
Quantitative cryoglobulin immunoglobulin G	53 mg/dL	18 mg/dL
Quantitative cryoglobulin immunoglobulin M	56 mg/dL	23 mg/dL
Rheumatoid factor	95 IU/mL	<14 IU/mL
Hepatitis C viral load	24,597 IU/mL	<12 IU/mL

ceftaroline. Punch biopsy of the skin lesions was performed on hospital day #5 with H&E staining yielding findings consistent with leukocytoclastic vasculitis, with histopathology demonstrating perivascular and interstitial infiltrates of polymorphonuclear cells with neutrophil dust (Figure 1). Laboratory studies, recommended by nephrology, from the same time period were notable for qualitatively positive cryoglobulins, low serum complement levels, including C3 of 50 mg/dL and C4 of 10 mg/dL, positive hepatitis C viral load of 24,597 IU/mL and negative anti-nuclear cytoplasmic antibodies. Quantitative cryoglobulins were elevated for Immunogolobulins A, G and M and rheumatoid factor was elevated at 95 IU/mL suggesting a mixed Type II cryoglobulinemia (Table 1). A urinalysis demonstrated proteinuria and microscopic hematuria with urine protein/creatinine ratio of 0.7, concerning for possible glomerulonephritis, although a renal biopsy was not performed as the results were felt to be unlikely to change the patient's clinical management.

Computerized tomography (CT) of the chest on hospital day #3 demonstrated the presence of septic pulmonary emboli as well as a sternomanubrial abscess with underlying sternal osteomyelitis. On hospital day #6, he underwent incision and drainage of the sternal fluid collection with cultures from the site also growing MRSA. The collection was felt to be a consequence of his prolonged MRSA bacteremia in the setting of his previous sternotomy. The patient denied injecting substances into his sternum. On hospital day #8, he developed hematochezia with decrease in his hemoglobin to 7.4 g/dL. CT of the abdomen and pelvis with contrast demonstrated evidence of diffuse colitis. Stool testing for *Helicobacter pylori* antigen, *Clostridium difficile*, and other enteric pathogens by polymerase chain reaction was negative. On hospital day #9, he underwent a colonoscopy which demonstrated rectal, sigmoid and descending colonic mucosa with edema, erythema, granularity, friability and global oozing of blood consistent with colonic ischemia. Biopsies were not obtained due to concerns for high-risk of

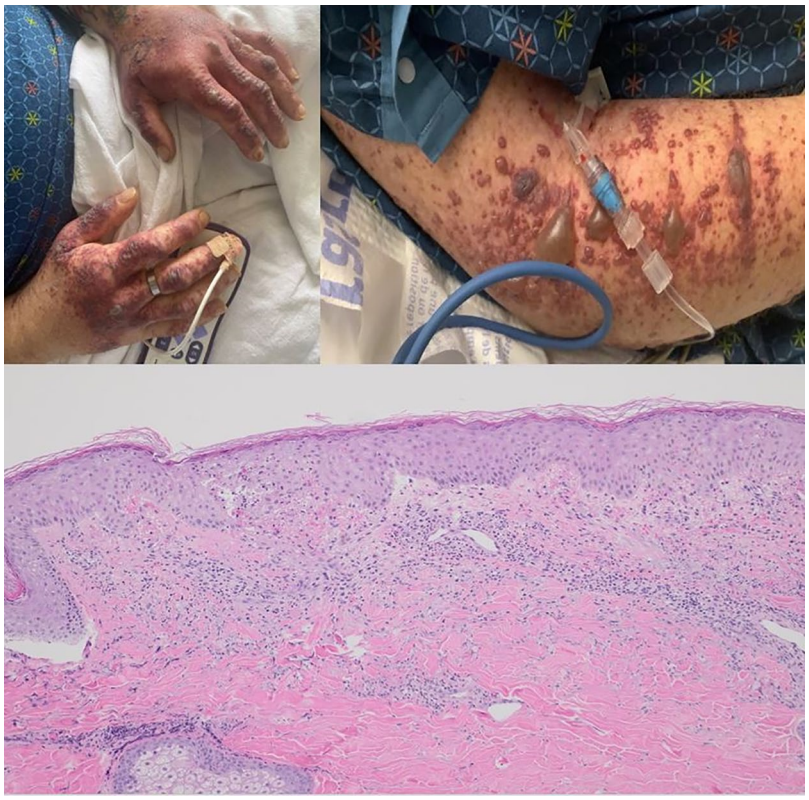

Figure 1. Case #1: Top panels demonstrating palpable purpura with tense overlying bullae throughout bilateral upper and lower extremities. Bottom panel with H&E staining from a punch biopsy at 10 times magnification demonstrating neutrophilic spongiosis, superficial dermis with perivascular and interstitial infiltrate of neutrophils, dust of neutrophils and extravasated erythrocytes.

perforation in the setting of possible ischemia. The hematochezia was managed conservatively with bowel rest leading to complete resolution of symptoms by hospital day #15.

Differential diagnosis for the etiology of the cryoglobulinemic cutaneous leukocytoclastic vasculitis with suspected renal and colonic involvement included the patient's history of active hepatitis C, drug reaction to vancomycin or a complication of endocarditis.[4,5] There was significant discussion by the hospital's multidisciplinary endocarditis team regarding whether to treat the hepatitis C while the patient was hospitalized due to the concern that it may be contributing to the vasculitis. However, his renal function, hematochezia and skin findings began improving while he was on antibiotic therapy and the team consensus was that the cryoglobulinemic vasculitis was most likely secondary to the underlying endocarditis. He was treated with intravenous daptomycin and ceftaroline from hospital day #3 to hospital day #13 until blood cultures were documented negative for 72 hours based on data that has demonstrated mortality benefit for patients with MRSA bacteremia treated with this regimen when compared to standard of care monotherapy.[6] He was then transitioned to daptomycin monotherapy to complete a total of 6 weeks of intravenous antibiotic treatment from blood culture clearance. He remained inpatient until hospital day #52 at which time he was discharged with complete resolution of the skin findings, improvement in his serum creatinine to 0.99 mg/dL and no further hematochezia. Treatment of hepatitis C was ultimately deferred to the outpatient setting.

Case 2

A 31-year-old female with history of substance use disorder, injection drug use and multiple prior episodes of MRSA tricuspid valve endocarditis, mostly recently ~6 months prior to this hospitalization presented to the hospital in March

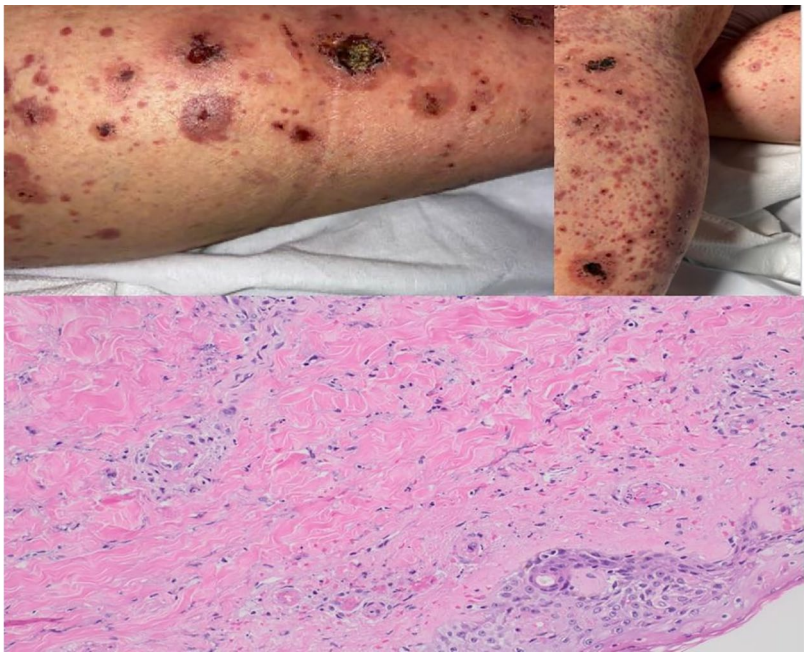

Figure 2. Case 2: Top panels demonstrating purpuric ulcerations over bilateral lower extremities. Bottom panel with H&E staining from a punch biopsy at 20 times magnification demonstrating superficial dermal blood vessels plugged with fibrin thrombi.

2022 with 1 week of fever, chills, lower extremity swelling and shortness of breath. On admission, laboratory studies were notable for a white blood cell count of 16,860/μL, hemoglobin 13.8 g/dL, platelet count of 164,000/μL, serum creatinine of 0.92 mg/dL, CRP of 200.6 mg/L and ESR of 30 mm/hr. Admission blood cultures grew MRSA (Table 1). CT of the chest obtained on presentation demonstrated septic pulmonary emboli. TTE on hospital day #1 demonstrated a vegetation present on the anterior leaflet of the tricuspid valve with a massive amount of tricuspid regurgitation causing significant right ventricular remodeling. On presentation she had painful and pruritic purpuric ulcerations along the bilateral lower extremities (Figure 2). Punch biopsy of a skin lesion was obtained on hospital day #8 (the patient declined to undergo biopsy earlier in the hospitalization) and demonstrated vasculitis with features of coagulopathy, with histopathology showing fibrin thrombi in dermal blood vessels (Figure 2). Laboratory studies at the time of the biopsy were notable for normal serum C3 of 97 mg/dL, and low serum C4 of 4 mg/dL, qualitatively positive cryoglobulins and negative antinuclear cytoplasmic antibodies. Quantitative cryoglobulins were elevated for Immunogolobulins A, G and M and rheumatoid factor was negative suggesting a mixed Type III cryoglobulinemia (Table 1). Urinalysis was notable for trace blood and no proteinuria. Hepatitis C antibody was positive but the patient's viral load was undetectable.

Differential diagnosis for the etiology of the cryoglobulinemic vasculitis included the patient's endocarditis or prior levamisole exposure, although levamisole was not detected in the patient's comprehensive urine drug screen obtained at the time of admission. The consensus of the hospital's multidisciplinary endocarditis team was that the vasculitis was most likely secondary to the underlying endocarditis.

The patient was initially treated with intravenous daptomycin and ceftaroline from hospital day #2 to hospital day #10 until blood cultures were documented as negative for 72 hr.[6] She was then transitioned to Daptomycin monotherapy on hospital day #11 with a plan for 6 weeks of treatment from blood culture clearance. On examination her skin lesions very slowly improved with antibiotic therapy; however, the patient reported significant ongoing pain. As a result, she was treated

with an ~10 day tapered course of prednisone from hospital day #10 to hospital day #20 with mild improvement in her pain and no worsening of her clinical status. She ultimately completed the last 7 days of antibiotic treatment with intravenous vancomycin as daptomycin has been associated with acute generalized exanthematous pustulosis and there was some concern this antibiotic may have been delaying her skin healing.[7]

She was ultimately discharged on hospital day #52 with ongoing improvement in her skin ulcerations which were in various stages of healing with no development of new lesions for ~5 weeks.

Discussion

Although cryoglobulinemia is reported as a known complication of endocarditis due to the development of circulating immune complexes, there are few published reported cases of cryoglobulinemic vasculitis associated with infective endocarditis. One 1952 study reported the presence of cold precipitable serum globulins in 42 of 50 patients with subacute bacterial endocarditis.[8] An additional study from 1975 found circulating serum cryoglobulins in 19 of 20 individuals with infectious endocarditis.[3] However, the presence of circulating cryoglobulins does not always correspond to a clinically significant vasculitis. In one series of 81 patients with chronic active hepatitis C, 45.7% of patients had detectable serum cryoglobulins but only 12.3% had signs and symptoms of vasculitis.[9]

The existing, albeit limited, literature regarding cryoglobulinemic endocarditis in vasculitis suggests that treatment of the endocarditis can resolve the vasculitis.[10] Spindel *et al.*[11] reported a case of a patient who presented with a purpuric rash while undergoing treatment for MSSA tricuspid valve endocarditis with biopsy of the skin lesions consistent with leukocytoclastic vasculitis. Another reported case initially presented as a purpuric rash several weeks after hospitalization for COVID-19 infection. Skin biopsy revealed leukocytoclastic vasculitis, and the patient was subsequently found to have MRSA bacteremia and a mitral valve vegetation.[12] In both of these cases, antibiotic therapy for endocarditis resulted in improvement of the cutaneous vasculitis.

In other cases, cryoglobulinemic vasculitis may be misdiagnosed as being a primary auto-immune disorder rather than the result of an underlying infection. Lamba *et al.*[13] and Agarwal *et al.*[14] reported separate cases of patients who presented with mixed cryoglobulinemia that were treated with high-dose steroids with worsening of their clinical condition before ultimately being diagnosed with infectious endocarditis. In both cases, treatment of the endocarditis resolved the underlying cryoglobulinemic vasculitis.

It appears that a number of organisms can lead to development of endocarditis associated cryoglobulinemic vasculitis as published reports include patients infected with MSSA, MRSA, *Enterococcus spp.*, *Streptococcus spp.*, Coagulase negative *Staphylococcus, Kingella Kingae and Bartonella*.[1–16]

While there have been multiple examples of individually reported cases, to the authors knowledge the only other case series of cryoglobulinemic vasculitis in the setting of endocarditis was published by La Civita *et al.*[15] in 2002. Notably, in that series the two case were identified 5 years apart.

Here, we present two patients with MRSA tricuspid valve endocarditis with diffuse petechial and purpuric skin lesions, both subsequently found to have positive serum qualitative cryoglobulins and skin biopsy findings consistent with vasculitis. Interestingly, these two patients presented to the hospital only 13 days apart. Although both patients had other possible causes of vasculitis, both patients also improved with antibiotic therapy for their endocarditis, including one patient with chronic active hepatitis C that did not receive treatment for this while inpatient. One patient was treated with a 10-day course of prednisone without progression of their infection. The other patient improved without glucocorticoid therapy. In addition, one patient had urine studies suggestive of possible glomerulonephritis and imaging and colonoscopy findings suggestive of diffuse colitis with no other etiology. These findings suggest that patients with cutaneous manifestations of cryoglobulinemic vasculitis from endocarditis may also develop other sites of end-organ involvement.

Notably both patients had a history of injection drug use and prior infectious endocarditis within the last 6 months prior to their index hospitalizations. It's possible that both patients had smoldering infection that allowed for the development

of circulating immune complexes which as discussed above appear to be more common in patients with subacute endocarditis.[8,9] *Staphylococcus aureus* endocarditis tends to present acutely with sudden-onset of symptoms, associated sepsis and high-mortality.[17] However, both of our patients and other reported cases of *Staphylococcus aureus* endocarditis associated with cryoglobulinemic vasculitis presented after several weeks of symptoms or with recent prior endocarditis.[11,12]

Implications for clinical care

Providers should have a high index of suspicion for endocarditis in patients presenting with new cryoglobulinemic vasculitis, particularly if the individuals have underlying risk factors such as injection drug use, prior endocarditis or the presence of prosthetic intracardiac material as delayed diagnosis can lead to high rates of mortality.[15,17] In addition to cutaneous findings, patients may develop new glomerulonephritis or colitis highlighting the importance of multidisciplinary coordination of care.

The authors would advocate that all patients diagnosed with cryoglobulinemic vasculitis have blood cultures collected to rule out the possibility of underlying endocarditis contributing to their presentation. Providers can also consider the possibility of vasculitis in patients with known endocarditis who develop typical cutaneous manifestations or other features of the disease such as glomerulonephritis. While there is some risk associated with false positive cultures this is greatly outweighed by the potential risk of a missed diagnosis and inappropriate treatment with immunosuppression. Providers could also consider the utility of screening transthoracic echocardiography before starting immunosuppression, particularly in patients with an uncertain diagnosis or risk factors for endocarditis. In light of the increase in injection drug-use associated endocarditis in the United States and the challenges patients with endocarditis have gaining access to surgery providers may encounter more cases of endocarditis associated cryoglobulinemic vasculitis.[18–20]

In this series, and others, targeted antibiotic therapy for endocarditis resulted in complete resolution of the cutaneous manifestations of the vasculitis. In patients with endocarditis and co-morbid hepatitis C it may be reasonable to treat the endocarditis first to see if the symptoms of vasculitis improve before pursuing treatment of hepatitis C particularly given that it can be difficult to obtain the appropriate medication while inpatient due to cost. In case #1 the patients was started on hepatitis C treatment ~2 weeks after discharge from the hospital. Finally, in patients with severe symptoms related to the cutaneous manifestations of cryoglobulinemic vasculitis, short courses of low-dose prednisone may be safely administered without progression of infection.

Declarations

Ethics approval and consent to participate

Approval was obtained from the University of Kentucky Intuitional Review Board (Number 71514).

Consent for publication

Verbal informed consent was obtained from the patients for the publication of this report.

Author contribution(s)

Laura Josephson: Conceptualization; Methodology; Writing – original draft; Writing – review & editing.

Virgilius Cornea: Data curation; Resources.

Bobbi Jo Stoner: Writing – original draft; Writing – review & editing.

Sami El-Dalati: Conceptualization; Methodology; Supervision; Writing – original draft; Writing – review & editing.

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