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CASE REPORT

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CLINICAL CASE SERIES: EDITOR'S HIGHLIGHTS

LVAD Vasculitis Case Series

Suggestion of a New Fatal LVAD-Related Phenomenon

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ABSTRACT

Left ventricular assist devices (LVADs) are surgically implanted mechanical devices indicated for patients with advanced heart failure and are known to come with several complications. Here we present a case series, and review 1 documented report, of LVAD vasculitis, a presumed new LVAD immune/humoral related phenomenon. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2021;3:1013–7) © 2021 Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

CASE 1

A 59-year-old man with nonischemic cardiomyopathy and a HeartMate II left ventricular assist device (LVAD) (Abbott Laboratories) (implanted 5 years before) presented with several days of weakness, fatigue, hemoptysis, and dyspnea.

Three months before, he was seen by a dermatologist for an unspecified maculopapular rash of the lower extremities, and later developed microscopic hematuria and acute kidney injury (AKI). On admission, he was without rash, but had AKI, a supratherapeutic international normalized ratio, and developed acute hypoxic respiratory failure requiring

LEARNING OBJECTIVES

- To understand the importance of immediate skin biopsy in LVAD recipients who present with maculopapular/petechial rash, especially if underlying vasculitis is suspected.
- To understand the need for thorough investigations in LVAD recipients who are diagnosed with any form of a vasculitis.
- To be able to treat LVAD vasculitis (biopsy-confirmed, systemic vasculitis in LVAD recipients) through appropriate steroid/immune therapy, in combination with other interventions/therapies that target the etiology of the vasculitis.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

AKI = acute kidney infection

C. jeikeium = *Corynebacterium jeikeium*

HLA = human leukocyte antigen

LCV = leukocytoclastic vasculitis

LVAD = left ventricular assist device

PIGN = postinfectious glomerulonephritis

S.aureus = *Staphylococcus aureus*

immediate mechanical ventilation. Imaging demonstrated pulmonary infiltration, bronchoscopy confirmed alveolar hemorrhage, and sampling revealed elevated p-anti-neutrophil cytoplasmic antibody levels (1:5,120) and positive reflexive myeloperoxidase testing. The patient received a diagnosis of secondary microscopic polyangiitis, and respiratory cultures grew methicillin-resistant *Staphylococcus aureus (S.aureus)* (appropriately treated with vancomycin). He later experienced spontaneous bleeding requiring transfusion, persistent respiratory failure requiring tracheostomy, and worsening renal failure (peak creatinine 3.3 mg/dL). Renal and pulmonary biopsies were not performed because of the patient's unstable condition. He was initiated on steroids, intravenous immunoglobulin, and subsequent rituximab, and renal function normalized in 1 week. Unfortunately, the patient later developed Klebsiella bacteremia, septic shock, and multiorgan failure, and died (hospitalization 8 weeks).

CASE 2

A 62-year-old man with ischemic cardiomyopathy and a HeartMate II LVAD (implanted 4 years before) and recurrent driveline infections (methicillin-sensitive *S.aureus* and *Enterococcus faecium*) on amoxicillin-clavulanate for long-term suppression presented to the hospital with a 1-week history of fevers and a 3-day rash. Petechial, maculopapular lesions were present on the lower extremities and buttocks. AKI was present, and erythrocyte sedimentation rate and C-reactive protein levels were elevated. In-hospital class I human leukocyte antigen (HLA) testing was positive for B7, B13, B27, B42, B48, B60, and B81, and was weakly positive for B8, B41, B55, B67, B76, and B82. Class II HLA testing was negative (no prior HLA testing). Skin biopsy revealed leukocytoclastic vasculitis (LCV) and blood cultures grew *Corynebacterium jeikeium* (*C. jeikeium*), which was appropriately treated with doxycycline. Positron emission tomography imaging showed new, increased moderate metabolic activity surrounding the LVAD inflow cannula. One week later, creatinine peaked at 4.1 mg/dL but steadily decreased after initiation of prednisone 60 mg daily. Renal biopsy was consistent with postinfectious glomerulonephritis (PIGN). The patient was discharged (hospitalization 5 weeks) on a course of prednisone and doxycycline. After 2 months, all symptoms and renal function normalized, and his health remained at baseline several months thereafter.

TABLE 1 Characteristics of 4,130 LVAD Recipients From 26 Hospital Systems in the IBM Explorys Database

	LVAD Recipient and No Vasculitis (n = 3,790)	LVAD Recipient and Vasculitis (n = 340)	*P* Value
Age >65 y	1,860 (49)	180 (53)	0.17
Male	2,740 (72)	270 (79)	0.0047
White	2,810 (74)	280 (82)	0.00001
Coronary artery disease	2,860 (75)	290 (85)	0.000045
Myocardial infarction	3,470 (59)	220 (65)	0.00001
Stroke	720 (19)	100 (29)	0.00001
Diabetes	1,910 (50)	230 (68)	0.00001
Hypertension	3,100 (82)	320 (94)	0.00001
Smoker	1,670 (44)	170 (50)	0.035
Sepsis	1,050 (28)	160 (47)	0.00001

Values are n (%).
LVAD = left ventricular assist device.

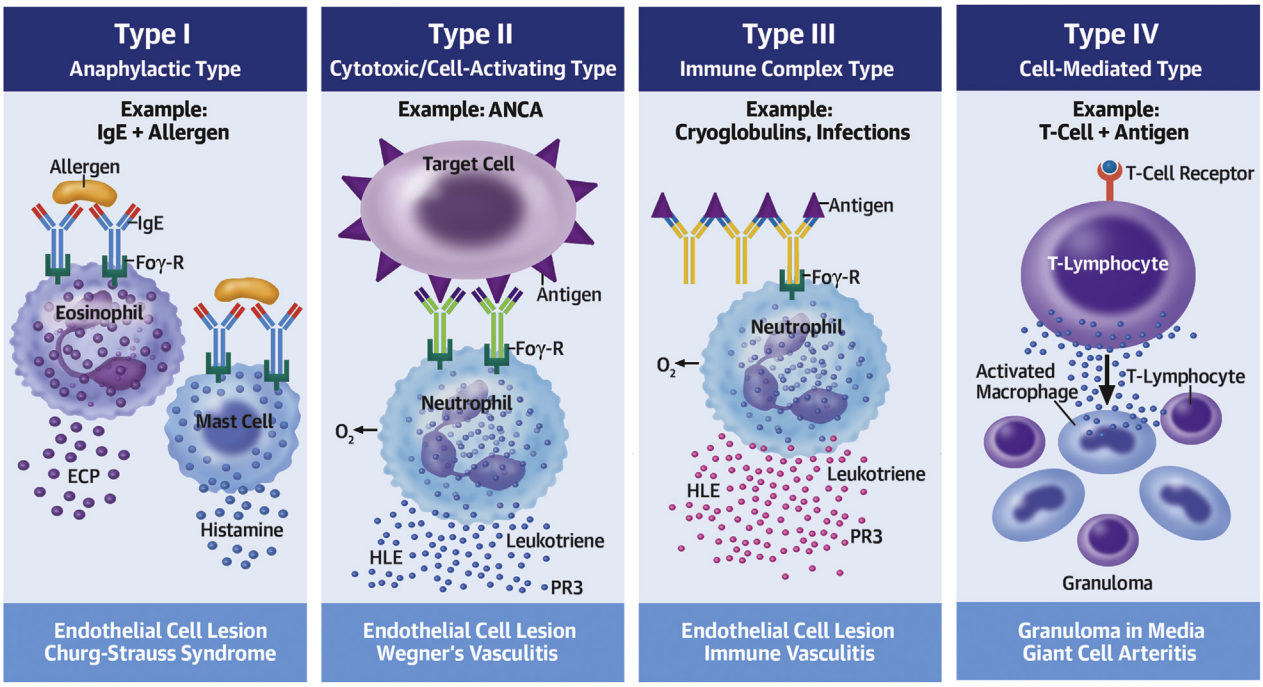
CASE 3

A 70-year-old man with ischemic cardiomyopathy and a HeartMate III LVAD (implanted 1 year before), and stage IIIA chronic kidney disease with baseline creatinine of 2.2 mg/dL presented to the hospital with several days of chills, fatigue, lethargy, and gross hematuria. Three months before presentation he developed an unspecified maculopapular rash of the upper extremities, 2 months before presentation he was admitted with interstitial lung findings and was treated for presumed pneumonia, and 3 weeks before presentation he had hematochezia. The rash, dyspnea, and hematochezia resolved before his presentation. Admission diagnostics revealed anemia, AKI, and methicillin-sensitive *S.aureus* bacteremia, and he was appropriately treated with blood transfusions and cefazolin. After 10 days, he developed a petechial rash again, but was over the lower extremities. Skin biopsy revealed LCV. His renal function continued to gradually worsen (peak creatinine 6.98 mg/dL) requiring hemodialysis and renal biopsy demonstrated immunoglobulin A glomerulonephritis as a PIGN. Steroids were never started as AKI was believed to be solely infectious. He remained on dialysis and later developed an additional *Klebsiella oxytoca* infection and diffuse intravascular coagulation, and he died (hospitalization 14 weeks).

DISCUSSION

LVADs are durable, surgically implanted mechanical devices that support the hearts of patients with advanced heart failure. However, these devices come with their own complications, such as hemodynamic alterations, thromboembolic phenomena,

FIGURE 1 Vasculitis and the Related Types of Immune-Mediated Interactions



ANCA = antineutrophilic cytoplasmic antibody; ECP = eosinophilic cation protein; Eos = eosinophil; $Fc_{\varepsilon}R$ = immunoglobulin E receptor; FcγR = immunoglobulin G receptor; HLE = human leukocyte elastase; IgE = immunoglobulin E; Ly = lymphocyte; MO = macrophage; O2- = superoxide/oxygen free radical; PR3 = proteinase 3; T-Ly = T-lymphocyte.

coagulopathy, and humoral sensitization (antibody development against specific human antigens) (1).

We present 3 LVAD recipients affected with vasculitis within the past 3 years at University Hospital Cleveland Medical Center (proper ethical oversight obtained). We defined LVAD vasculitis as the biopsy-confirmed presence of any vasculitis, with systemic (multiorgan) dysfunction, in an LVAD recipient. All 3 cases fit this description. All other predisposing factors or causes of vasculitis (hematologic, dermatologic, infectious, medication-induced, or connective tissue diseases and malignancy) were ruled out through thorough history, examination, and investigative laboratory data/cultures. Transesophageal echocardiography ruled out endocarditis. All positive tests are reported in the previous text. All patients were on the same medications for several months to years, with no new medications before initial symptoms.

All patients developed rash before hospitalization and vasculitis (all infectious-related) with systemic end-organ dysfunction (all with renal failure). All clinical courses, however, were not uniform. The initial rashes of patients 1 and 3 were not biopsied on outpatient evaluations. Additionally, they were without in-hospital HLA testing, although prior testing was negative. In our third case, the patient's rash reoccurred (days after cefazolin) and was biopsied. Although medication-induced vasculitis was considered, there was no improvement in end-organ dysfunction even weeks after discontinuing cefazolin, and skin biopsy demonstrated predominant neutrophilic infiltration (without predominant mononuclear infiltrates or prominent eosinophilia) (2) consistent with LCV.

Despite variations in cases 1 and 3, both presented months after the initial rash, with multiorgan failure and subsequent mortality. If skin biopsies were performed and steroid/immunotherapy was implemented sooner, less ambiguity would prevail, with potentially less fatalities. Thus, we share this first case series on LVAD vasculitis to highlight this under-recognized and rare phenomenon, because there are no current guidelines on its evaluation or management.

VASCULITIS. Vasculitis is any inflammatory vessel disease that is definitively diagnosed on biopsy. A maculopapular rash is a heralding sign, and rash was noted first in all of our cases, and in one other

documented report of LVAD vasculitis (3). LCV is a small-vessel vasculitis defined as neutrophilic inflammation, which results from immune complex deposition (type III reaction, **Figure 1**) and can be idiopathic or caused by other systemic vasculitides, connective tissue diseases, malignancy, paraprotein disorders, infections, or medications. LCV can be localized to the skin, or can be systemic involving the skin and other organ(s), with mainstay treatment including steroids (4).

Microscopic polyangiitis is a type II systemic, myeloperoxidase-antineutrophilic cytoplasmic antibody-associated vasculitis. It has several causes, but infections are a major differential (5), and therapy includes steroids and immunomodulators (eg, rituximab).

To further evaluate the relationship between vasculitis and LVAD recipients, we queried a large, multi-institutional electronic health care database (Explorys). The Explorys platform provides records from 26 major US health care systems with over 50 million patients. For our retrospective cohort analysis of baseline characteristics (**Table 1**), of the 4,130 LVAD recipients analyzed, 340 had vasculitis. Higher proportions of cardiovascular disease, smoking, and sepsis were noted in the vasculitis group. As this trend of risk in these LVAD recipients is similar to that in the general population, we found further credence toward infection as the primary etiology of LVAD vasculitis.

INFECTIONS AND POTENTIAL IMMUNE FACTORS. The impact of LVAD implantation on the cell-mediated and humoral immune systems is speculated to be one factor that predisposes recipients to infectious complications (**Figure 1**). Infections are associated with immune-mediated interactions (commonly type III) in certain vasculitides through the stimulation of antigen presentation, B cells, and prime neutrophils (6,7). Thus, one may deduce that the cumulative presence of an LVAD and an infectious state augment humoral stimulation/sensitization, creating the ideal milieu for LVAD vasculitis. However, this presumption requires further investigation, and to date, there is no known/established relationship between class I HLA and LCV.

In all noted LVAD cases with LCV (3), acute gram-positive infection was the determined cause. *C.jeikeium* is known to be a multidrug resistant organism that may cause various infections (8). However, no cases have reported *C.jeikeium* causing LCV, let alone in an LVAD recipient. Furthermore, as LCV results from immune complex-mediated inflammation and PIGN from immune complex glomerular injury, we presume type III interactions in all LCV cases (3), as all involved an infectious etiology.

RENAL FAILURE. In our series, when AKI was present, daily increases in creatinine averaged from 0.2-0.5 mg/dL. Full renal recovery occurred in 2 of 3 patients, both of whom received steroids/immunological therapy in addition to antibiotics. With steroid/immune therapy, there was immediate, consistent daily improvement until normalization, while the lack thereof led to persistent renal failure (3).

MORTALITY. Including the case by Bunker et al. (3), all but 1 patient died of LVAD vasculitis. The characteristics associated with survival among these patients include early presentation, early biopsy, and combined antibiotic and steroid/immune therapy. Considering the little known of LVAD vasculitis and its current high mortality rates, awareness is imperative.

CONCLUSIONS

To date, LVAD vasculitis remains a poorly described and under-recognized phenomenon. Of the aforementioned reported and documented cases of LVAD vasculitis (3) (most common type: LCV), all had rash as a heralding sign, all had acute infection (most common type gram positive), all had renal failure (most common type PIGN), and all but 1 died (mean hospitalization 9 weeks).

Given the observed clinical courses and mortality, we recommend that all LVAD recipients with a new petechial/maculopapular rash undergo immediate biopsy with no delay. We also recommend a full course of steroid/immunotherapy in addition to antibiotics for infection-induced LVAD vasculitis.

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