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Case Report

Eosinophilic granulomatosis with polyangiitis in a continuous flow left ventricular assist device patient: a case report and review of literature

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ABSTRACT

Eosinophilic granulomatosis with polyangiitis (EGPA), also known as Churg–Strauss syndrome (CSS), is a rare autoimmune disease with an estimated incidence of approximately 0.11 to 2.66 new cases per 1 million people per year and an overall prevalence of 10.7 to 14 per 1 million adults [1]. No gender predominance or ethnic predisposition has clearly been demonstrated in CSS [1]. Most of the patients are misdiagnosed over a period of time prior to being correctly classified with the disease. Here, we report the complex case of a 64-year-old African American man with advanced heart failure who received a left ventricular assist device (LVAD) and was subsequently diagnosed with EGPA. EGPA is a clinical syndrome that is associated with sequelae that can negatively add to the morbidity associated with LVAD placement.

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1. Introduction

Churg–Strauss syndrome (CSS) was first described in 1951 by J. Churg and L. Strauss as a form of disseminated necrotizing vasculitis with extravascular granulomas occurring among patients with asthma and tissue eosinophilia [1]. Called Churg–Strauss syndrome for many years, this condition has now been recognized by the 2012 revised nomenclature for vasculitides as eosinophilic granulomatosis with polyangiitis (EGPA) [2]. The histological lesions observed by Churg and Strauss in most of the affected sites were extremely severe. Most specimens were obtained from autopsy cases; therefore, the tissue samples were large specimens, which facilitated the detection of the histological markers of EGPA. In addition, glucocorticoid treatment was not available at that time. Glucocorticoids have dramatically changed the prognosis of EGPA [3]. The knowledge of EGPA has recently evolved, and now, newer targeted agents have been developed to address the disease, such as the monoclonal antibody mepolizumab [4]. Antineutrophil cytoplasmic antibodies (ANCA) have been found in a proportion of EGPA patients; therefore, EGPA has been included in the spectrum of ANCA-associated vasculitis together with granulomatosis with polyangiitis (Wegener granulomatosis) and microscopic polyangiitis [5].

2. Case report

The patient is a 64-year-old man with a past medical history of coronary artery disease status post coronary artery bypass grafting, ischemic cardiomyopathy status post biventricular implantable cardioverter defibrillator on home milrinone, atrial flutter status post ablation with a history of left atrial appendage thrombus and left ventricular thrombus on anticoagulation, type II diabetes mellitus (T2DM), lower extremity peripheral arterial disease (PAD), stage III chronic kidney disease, and history of angioedema who presented with acute decompensated heart failure and cardiogenic shock requiring inotropic support. He was hospitalized in the intensive care unit. He had been hospitalized several times prior with dyspnea. The repeated hospitalizations, in addition to the need for inotropic support, prompted a workup for advanced heart failure therapies. He was subsequently presented at the hospital's medical review board for consideration of advanced therapies. At the time of presentation, he had a cardiac index of 2.00 L/min/m^2 on milrinone therapy. He had a leukocytosis with a peripheral eosinophilia of 11.6% but no pruritis, no foreign travel, and no infectious signs or symptoms. The patient had a peripheral eosinophilia during prior hospitalizations for acute decompensated heart failure as well. Following the recommendation of the medical review board, he underwent bilateral femoropopliteal bypasses for severe PAD and then was subsequently approved for left ventricular assist device (LVAD) as destination therapy (DT). A HeartMate II axial flow LVAD was placed.

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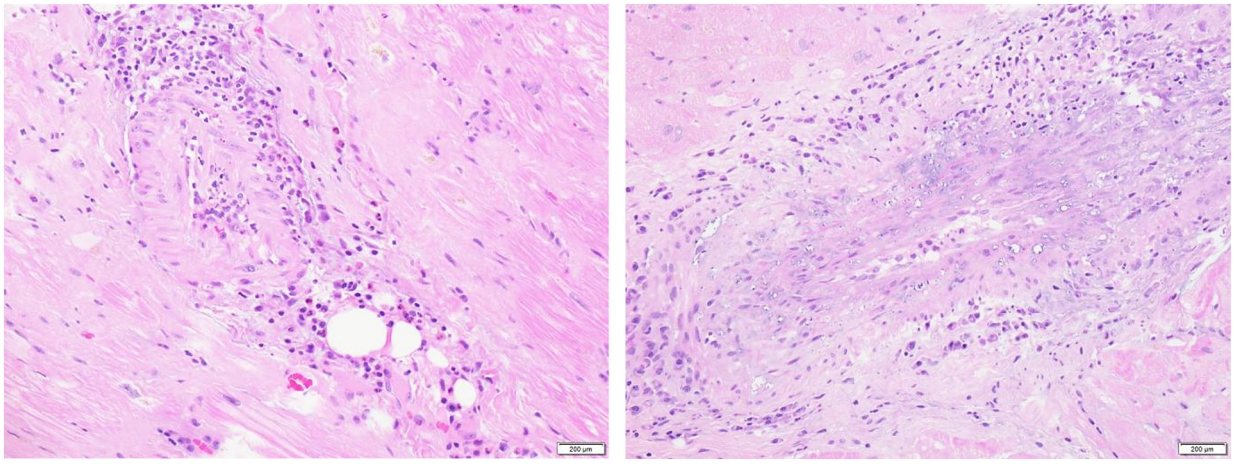


Figs. 1 and 2. Both specimens are from the left ventricular core [hematoxylin and eosin (H&E), 40×]. The images demonstrate perivascular and intramural inflammatory infiltrate with easily identified eosinophils. There is also the presence of both intimal thickening and luminal inflammatory cells, consistent with vasculitis.

At the time of LVAD placement, a core of left ventricular tissue was obtained as part of standard practice. Microscopic examination revealed perivascular inflammatory infiltrate with easily seen eosinophils (Fig. 1). Inflammatory infiltrate was also seen in the wall of midsized vessels (Fig. 2), a sign of vasculitis. However, at that time, due to lack of serology testing, vasculitis was not called. The patient had an uneventful postoperative course and was discharged from the hospital. In the outpatient setting, he later had a worsening of renal function associated with hematuria, and a renal biopsy was obtained. Microscopically, there was focal segmental necrosis, suggestive of an acute process, along with fibrocellular crescents and 60% interstitial fibrosis, indicating chronicity (Fig. 3A). Immunofluorescence was negative (Fig. 3B), consistent with chronic active pauci-immune segmental necrotizing glomerulonephritis with crescents.

Once the diagnosis of pauci-immune glomerulonephritis was made, the patient was treated with cyclophosphamide. He was subsequently taken off the medication due to a chest wall infection. It was retrospectively noted that his eosinophil count reduced to near normal levels on this medication and rapidly increased again with its withdrawal. Around the same time, he had numbness and tingling in his lower extremities and was treated for a peripheral neuropathy believed to be related to longstanding T2DM with gabapentin, with some relief of symptoms. His renal function worsened, and he subsequently developed end-stage renal disease (ESRD) and dialysis dependence. He subsequently developed clinical evidence of pump thrombosis and underwent a pump exchange. The pump was sent to Thoratec (Thoratec Corporation, Pleasanton, CA, USA) for analysis, where pump thrombosis in the impeller was confirmed (Picture 1). After the pump exchange, the patient then developed an acute pain in his left foot associated with a rapidly progressive gangrene (Picture 2). He required amputation, the amputated foot was sent to pathology for examination, and more evidence of vasculitis was noted (Figs. 4 and 5). At this juncture, due to the confluence of events and P-ANCA and anti-MPO antibody-positive tests, the medical team suspected that the vasculitis was associated with EGPA. Upon review of all his pathological specimens, he was diagnosed with EGPA and treated with corticosteroids. However, he had poor wound healing, likely a result of high-dose steroids, and developed an LVAD pocket infection. In addition, lactate dehydrogenase had again risen to 2.5× the upper limit of normal, suggesting another pump thrombosis event. The patient declined further invasive procedures, was made comfort care, and subsequently expired.

3. Discussion

There has been a rapid increase in the use of LVADs in the treatment of advanced heart failure [6]. The specific management of comorbidities in LVAD patients is an area where data are still emerging, and clinicians, albeit rarely, may encounter patients with EGPA. The condition may be diagnosed or undiagnosed at presentation. The patient presented in this clinical case was not initially diagnosed with EGPA. The definitive diagnosis was made over a period of time with corroborative information

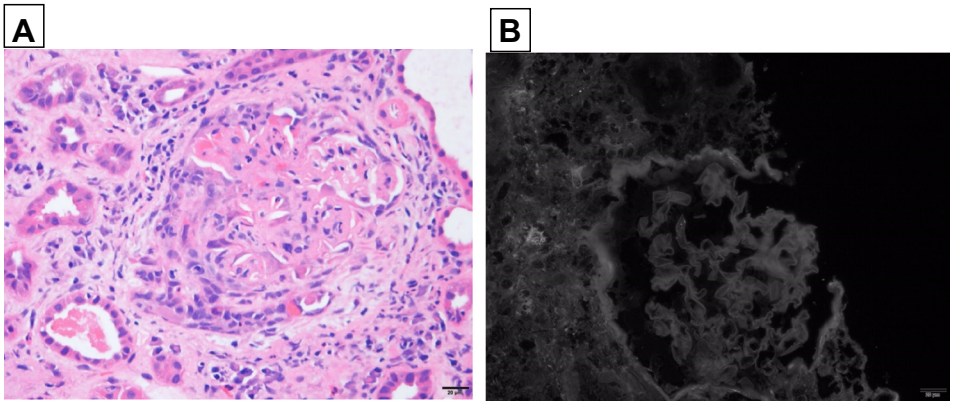
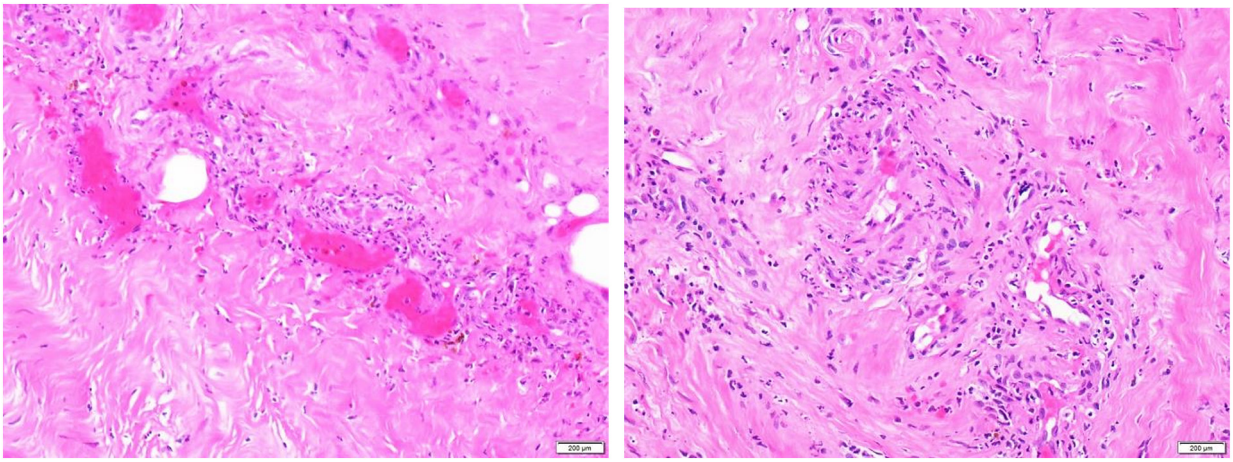


Fig. 3. (A) Glomerulus with segmental necrosis and fibrocellular crescent formation (H&E, 40×). (B) IgG immunofluorescence was negative (along with entire immunofluorescence panel) (IgG, 40×).



Figs. 4 and 5. Both specimens are from the amputated foot (H&E, 40×). The images demonstrate perivascular and intramural inflammatory infiltrates, which are features of vasculitis. The adjacent soft tissue has little inflammatory background.

from heart specimens, renal specimens, amputation specimens, and serologic testing.

There are three phases of EGPA [7]. The first phase is a prodromal phase that is characterized by allergic rhinitis, recurrent sinusitis, and nasal polyposis. The second phase is an eosinophilic phase in which there is eosinophilia in the peripheral blood and tissues without proven vasculitis. The third phase is the vasculitis phase associated with constitutional symptoms and vasculitis of small to medium-sized vessels. The vasculitic phase usually develops within 3 years of onset and can involve various organ and organ systems, such as the peripheral nervous system (mononeuritis multiplexa in 78% of patients), heart, and kidneys [8]. This patient was most likely in the eosinophilic phase of the disease at the time of placement of his LVAD. In this patient, the first allergic phase and asthma-like picture were taking place at the same time as the patient's heart failure exacerbations, and his episode of angioedema was attributed to the use of angiotensin-converting enzyme inhibitors prescribed for heart failure. The eosinophilic phase coincided with the worsening of his heart failure into advanced heart failure, and it is unclear if there was cardiac involvement of EGPA that precipitated the worsening of his heart failure. At the time of LVAD placement, the prodromal phase had passed, and he was implanted at a time where he had eosinophilia but none of the clearer manifestations of the vasculitic phase to make the diagnosis of EGPA more certain.

Cardiac involvement portends a poor prognosis in patients with EGPA, representing up to 50% of the mortality related to the disease [9]. The mechanism or involvement is related to vasculitis or the coronary arteries and direct eosinophilic infiltrate of myocardium. The patient in this vignette carried a diagnosis of ischemic cardiomyopathy which may have been mediated by unrecognized EGPA activity. At the time of LVAD placement, eosinophils were present in the myocardial specimen obtained at the time of placement of the device which, in retrospect, raises the concern for an unrecognized infiltrative component of his cardiomyopathy. At that time, instead of EGPA, a descriptive diagnosis "Perivascular inflammatory infiltrate with easily seen eosinophils" was made.

The patient in this clinical vignette experienced three main adverse events related to EGPA after placement of his LVAD: progression of his associated pauci-immune glomerulonephritis resulting in ESRD and dialysis dependence, pump thrombosis, and amputation resulting from the associated vasculitis. Pauci-immune glomerulonephritis is known to rapidly progress to ESRD and is associated with anti-MPO antibodies [10], which were present in our patient. When the diagnosis of pauci-immune glomerulonephritis was made, the patient was treated with cyclophosphamide which also caused a brief remission in his EGPA as its withdrawal due to infection coincided with the worsening of his renal disease requiring dialysis. ESRD carries a high mortality risk in LVAD patients [11].

Thrombosis is a complication of eosinophilia [12], and eosinophilia was a contributing factor to the pump thrombosis seen on our patient that was confirmed to be present in the LVAD impeller by Thoratec. Several hypotheses have been proposed to link eosinophilia and thrombosis. Endothelial cells may be damaged by eosinophil peroxidase products, and these products along with eosinophil cationic protein and major basic protein can stimulate platelet activation and aggregation [13]. Eosinophils also express CD40 ligand, which is involved in thrombosis through amplification of the body's inflammatory response [14]. Finally, eosinophils store the coagulation initiator tissue factor (TF) in granules, which becomes exposed during activation [15]. TF exposure promotes migration of eosinophils and triggers activation of the extrinsic pathway of blood coagulation, leading to a prothrombotic state which is of concern in an otherwise normal patient and of even greater concern in patients with the added risk factor of stasis related to their LVAD.

There has been a previous case report of a patient with EGPA that had an LVAD implanted as a bridge to transplantation and then successfully underwent an orthotopic heart transplantation [16]. This case report is the first report, to our knowledge, of a patient with EGPA who received an LVAD as DT and then developed LVAD complications related to the disease process and treatment of EGPA. In addition, the morbidity associated with EGPA diminished the benefits of the LVAD placement. The complication of having an amputation and mobility limitation negatively impacted quality of life and was instrumental in the patient declining further invasive procedures and escalation of care. In conclusion, it is important to entertain the diagnosis of EGPA when treating patients with unexplained eosinophilia and heart failure, especially if advanced therapies such as LVADs are being considered, because of the vascular and thrombogenic complications associated with the disease.

The three authors of this paper, Lydia R. Engwenyu, MD; Amanda Tchakarov, MD; and Bihong Zhao, MD, PhD, have no conflicts of interest to report.

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