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Peer-Reviewed Case Report

Systemic Candidiasis and Cytomegalovirus Infection in the Setting of Artificial Cardiac Device Deployment

Manoj Thangam, MD[1], Bindu Akkanti, MD[2], Maan Malahafio MD[2], Sriram Nathan, MD[2], Indranee Rajapreyar, MD[2], Pranav Loyalka, MD[2], Biswajit Kar, MD[2], Igor D. Gregoric, MD[2]*

Center for Advanced Heart Failure[2], Department of Internal Medicine[1], University of Texas Health Science Center at Houston/Memorial Hermann Hospital – Texas Medical Center, Houston, Texas

* Corresponding author: Igor.D.Gregoric@uth.tmc.edu

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Abstract

Heart failure is a serious cause of morbidity and mortality worldwide. The advent of implantable cardiac assist devices has generated a new arsenal for treating severe heart failure. However, the potential ramifications of ventricular assist device (VAD) usage are not fully understood. Immune modulation resulting from VAD implantation is an area of growing research. Although we do not fully understand the mechanisms contributing to host immune alteration, changes in cytokine concentrations, deceased lymphocyte activity, and the local effects of device materials have been shown to down regulate immune function. Infection is a serious complication that affects prognosis in this patient population. Malnutrition, critical status, and cardiovascular stress are additional predisposing factors in this fragile group. Driveline and surgery-associated infections are the most commonly identified culprits. However, decreased host immune function facilitates atypical infections including systemic fungemia and viremia. This case is an interesting example of a VAD associated immune system compromise.

Keywords

Ventricular assist device; heart failure; infection; immune function

Background

Heart failure is one of the leading causes of morbidity and mortality worldwide and affects 1-2% of the population in developed nations.[1] Because of the rising incidence of heart failure, transplantation has become an increasingly necessary mode of definitive treatment. Unfortunately, the limited availability of donor hearts has left many patients seeking other treatment options.[1,2] Implantable devices have become a viable choice for patients suffering from heart failure requiring a bridge to transplantation or destination therapy.[2] However, many of the effects of ventricular assist devices (VADs) on the human body are not completely understood. One of the unexpected consequences of VAD usage is the alteration of immune systems after implantation.

Immune modulation related to cardiac pathology is a topic of ongoing research. Some studies have identified associations between heart failure and decreased immune function.[3] This is believed to result from increased inhibitory chemical mediators and immune suppressive T cell activity[3]. Other cardiac conditions including coronary artery disease, acute heart failure, and valvular dysfunction, have also been connected with decreased immune function.[3,4,5,6] Although the exact mechanism of immune modulation in each of these conditions is not understood, a bulk of evidence suggests that immune dysfunction contributes to disease processes and prolongs recovery.[3,4]

The effect of implantable devices on the immune system is a thriving area of investigation. Studies have shown that VAD utilization in heart failure patients is linked to decreased immunity. Because of the acute flux of chemical messengers after implantation, the net change in immune mediators results in decreased immune activity.[7] Mechanisms associated with VAD-induced immune comprise include increased immune inhibitory chemical mediators, decreased immune stimulatory messengers, reduced circulating lymphocytes, and direct interaction between device surfaces and host tissue.[7,8]

The time frame of immune compromise in these cases is not well understood. Studies have suggested that there is an acute decrease in immunity soon after VAD placement. However, the duration of this state requires further investigation.[9] Some research has evaluated the chemical mediators of immune function and found that these messengers return to baseline levels six months after implantation of the device.[9] These data suggest that there may be adaptive mechanisms for stabilizing immune function that is initially compromised by the implantation of VADs.

In states of immune compromise, patients are more susceptible to a myriad of infections. Viral and fungal infections are among the most common infectious etiologies seen in immune-compromised patients. Because immunecompetent hosts are generally able to fend off these infections, their presence has come to be associated with immunodeficient states. Heart failure and VAD implantation are not routinely recognized as states with decreased immune function. However, overwhelming evidence suggests that immune function is significantly diminished in these patients. We present this interesting case of VAD-associated

immunecompromise resulting in multiple infectious processes to serve as a reminder for the potential immune dysfunction occurring after VAD implantation.

Case Presentation

A 65-year-old Hispanic man presented to the emergency medical center with sub-sternal chest pain characterized as pressure with an intensity of nine out of ten. The non-radiating pain was ongoing over the past day and associated with diaphoresis, nausea, and vomiting. The patient's past medical history included hypertension, dyslipidemia, tobacco use, and coronary artery disease that required percutaneous intervention with a drug-eluting stent to the left anterior descending artery six years prior. The patient had no history of immune compromise, recurring infections, HIV, or hepatitis. He had an extensive family history of coronary artery disease, with an uncle and two cousins who succumbed to myocardial infarctions before the age of fifty. At the time of presentation, the alert patient was tachycardic, hypotensive, and tachypneic. His physical exam was notable for lethargy, diaphoresis, crackles at lung bases, and tachycardia. No murmurs, extra heart sounds, jugular venous distention, or peripheral edema were observed. Ophthalmoscopic examination was free of abnormalities.

The patient underwent laboratory and electrocardiographic evaluation, which revealed troponin elevation, liver transaminase increase, and an inferior ST segment elevation myocardial infarction. Transaminase elevation was credited to hepatic congestion occurring secondary to a cardiac event. At this time an elevated white blood cell count of 19000 per microliter was noted. There was no history of infection, immunodeficiency, likely sources of infection, or fever. The leukocytosis was attributed to a systemic inflammatory reaction syndrome and the patient was started on broad-spectrum antibiotics. He was urgently taken to the cardiac catheterization laboratory, where a complete occlusion of the right coronary artery (RCA) was identified. This discovery prompted deployment of a drug-eluting stent in the RCA. Although the patient tolerated the procedure well, over the course of the night, the patient complained of increasing chest pain and shortness of breath. A chest radiograph showed pulmonary edema. Diuresis with intravenous Lasix was initiated, but the patient's shortness of breath worsened with increasing need for oxygen supplementation. Because of his worsening condition, a trans-thoracic echocardiogram was performed. A new one-centimeter ventricular septal defect (VSD) along with a depressed ejection fraction of 45% was discovered. The patient's need for further cardiac support prompted intraaortic balloon pump placement and transfer to the Center for Advanced Heart Failure for evaluation for ventricular assist device implantation.

Upon arrival to our center, the patient was intubated and underwent TandemHeart (CardiacAssist, Inc.) peripheral ventricular assist device (pVAD) placement due to cardiogenic shock and an ischemic VSD. The patient continued diuresis while concurrently being weaned from vasopressor support for refractory cardiogenic shock. Leukocytosis improved with left ventricular support and the patient remained afebrile. Multiple blood, urine, and sputum cultures were performed with no growth. He was continued on broad-spectrum antibiotics due to pVAD implantation. VSD repair was planned to occur at a later date after

stabilization of the septal defect diameter and myocardial scarring that would facilitate closure device success.[10,12]

Two days after pVAD placement, the patient manifested his first fever of 101º F. New sputum, blood, and urine cultures were obtained and found to be negative. Procalcitonin levels were within normal range. Abdominal ultrasound was performed and showed no acute abnormalities or signs of infection. Seven days after TandemHeart placement, the patient's condition acutely worsened. Hypotension requiring vasopressors, increased ventilator dependence, worsening leukocytosis, and bilateral lung opacities observed on chest radiographs raised concern for acute respiratory distress syndrome. The antibiotic regimen was escalated to include meropenem, vancomycin, and micafungin. Bronchoscopy with bronchoalveolar lavage (BAL) was performed. Diffuse alveolar hemorrhage was diagnosed by obtaining progressively blood-tinged fluid in the lavage samples. The BAL fluid was cultured and found to contain yeast. Additionally, microthrombi were seen in the patient's toes along with falling platelet counts. This prompted concern for heparin-induced thrombocytopenia, which was confirmed by the presence of heparin-associated antibodies. Although bivalirudin was substituted for heparin, platelet depletion and clot formation persisted, and required therapy with plasmaphoresis. Pro-thrombotic activity was responsible for clot formation in the TandemHeart, which was exchanged for a CentriMag (Thoratec Corporation) blood pump for left ventricular support 10 days after TandemHeart placement. The patient was also noted to have elevated lipase levels that peaked 2,737 units per liter. Evaluation with computed tomography scans revealed hemorrhagic pancreatitis. Surgical and gastroenterology consultants deemed surgical intervention unnecessary.

Eleven days after the patient's myocardial infarction, percutaneous VSD repair was attempted three times without success. Because of severe biventricular failure and continued deterioration, the decision was made to implant a SynCardia Total Artificial Heart (TAH) (SynCardia Systems, Inc) as a bridge to definitive therapy. The operation was performed 19 days after the initial cardiac event. The patient had an arduous postoperative course complicated by prolonged intubation requiring tracheostomy, renal failure requiring hemodialysis, and persistent leukocytosis. Multiple bronchoscopies and BALs were performed with cultures repeatedly growing yeast. Speciation of the yeast noted in the BAL fluid was unsuccessful. The patient was treated with escalating regimens of antifungal therapy including fluconazole, micafungin, and amphotericin B. Concurrently, braod-spectrum antibacterial therapy with intravenous vancomycin and cefepime that was escalated to meropenem. Despite aggressive antimicrobial therapy, leukocytosis persisted in the face of clinical deterioration. Procalcitonin remained at normal values.

Forty-eight days after presentation, fungal blood cultures from the arterial and central venous catheters grew Candida galbarata. Seven days later, the patient complained of vision disturbances. Bilateral dilated eye exams performed by ophthalmologists revealed peripapillary vessels obscured by infiltrates and intraretinal hemorrhages consistent with cytomegalovirus (CMV). Polymerase chain reaction analysis revealed a viral load of 3,606 copies per milliliter, which prompted, initiation of ganciclovir. It was noted that Candida galbarata and CMV

were atypical infections in immunocompetent hosts. The presence of these infections supported an induced immunocompromised state. Reevaluation of HIV and hepatitis statuses found both to be negative. Despite aggressive treatment, the patient continued to deteriorate over several weeks and developed worsening hepatic failure, renal failure, ventilator dependence, and gastrointestinal bleeds. After discussion with the family, the patient was transitioned to palliative care and expired 88 days after admission.

Discussion

Artificial device implantation has unintended consequences on host immune systems. Processes that contribute to VAD-associated immune modulation were described by Itescu and colleagues to include protein absorption from device surfaces, material composition changes after implantation, mechanical stress on circulatory components, and effects of the material on host tissues.[7] That group also noted systemic and local T cell activation in response to VADs. The activated CD4 and CD8 T cells displayed increased CD95 expression, which is associated with T cell-mediated apoptotic pathways. The increased apoptosis was experimentally observed by noting elevated binding of annexin V to phosphatidylserine located on T cell membranes. Phosphatidylserine is an apoptosis-associated cell surface component for which annexin V has high affinity. Qualitative analysis of the chemical interaction between annexin V and phosphatidylserine serves as a marker for evaluating apoptotic activity. Additionally, Itescu's group reported B cell hyperactivity and increased major histocompatibility complex-targeted antibody production in VAD patients.[7] Overall, lymphocytic lineages including B cells, helper T cells, and cytotoxic T cells display altered function in this population.

Itescheu and colleagues correlated VAD related immune suppression with increased predisposition for Candida infections including albicans, parapsilosis, and galbrata sepsis. In their prevalence study evaluating 78 patients, 28% developed disseminated Candida infections compared to only 3% in a matched population without left VADs (LVADs). Also, cases of CMV viremia following LVAD implantation have been reported.[8,9]

Other studies have also shown increased B and T cell apoptosis in LVAD patients.8 Increased immune suppressive cytokine expression concurrent with down regulation of pro-inflammatory cytokines such as IL-2 and TNF-a has also been observed with concurrent increase in the immune suppressive cytokine IL-10.[10] Mitchell and colleagues contributed valuable information regarding the time frames of this immune modulation. Their work noted that decreased pathways of cellular immunity, pro-inflammatory cytokine synthesis, shifts in apoptotic pathways, and downregulation of immune proliferation were observed within 7 days after LVAD implantation. Other studies have noted decreased expression in genes related to immune activity as early as 1 day after implantation.[11]

Our patient received therapy with the TandemHeart pVAD temporarily and then underwent implantation of a TAH. He manifested fungal growth in blood cultures identified as systemic Candida galbarata 75 days after LVAD and 59 days after SynCardia TAH implantation. Furthermore, the patient developed CMV retinitis 9

days after the Candida was isolated. The presence of these microorganisms is highly suggestive of decreased immunity. Prior to his cardiovascular event, the patient was immunecompetent with no previous history of similar infections. Over the course of his treatment with these devices, his immune functions gradually deteriorated. While the waning of his immune function may be multifactorial, device implantation was a contributing component of his decline.

Although LVADs have been associated with decreased immunity, the effect of TAH placement on the immune system has not been well investigated. The fundamental mechanisms of immune dysfunction proposed by Itescheu and colleagues remain true in the presence of a TAH. Further investigations into the mechanisms of immune modulation concerning these devices are necessary. Our case serves as an example of immune comprise related to LVAD and TAH utilization. Although other etiologies may have contributed to the patient's decline, the waning of his immune function was a major source of his clinical deterioration and eventual demise. We hope this case serves as a reminder of artificial device-associated immune alterations and prompts early consideration of infectious etiologies related to immunocompromised states. Increased awareness of this phenomenon may serve to facilitate early identification of causative organisms and expedite targeted intervention.

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