

# Cytomegalovirus reactivation in left ventricular assist device patients: case series and literature review

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## Background

Cytomegalovirus (CMV) reactivation after placing left ventricular assist device (LVAD) is not a well-known entity with few cases reported in the literature. Here, we are presenting three cases of CMV reactivation after placing LVAD. A literature review of all reported cases in the literature was done.

## Case summary

Three cases of advanced heart failure with reduced ejection fraction (Stage D9) had placed (LVAD) at the American University of Beirut Medical Center, a tertiary care centre in Lebanon. Within the first 2 weeks after LVAD implantation, the three patients spiked a high-grade fever for which sepsis workup was done, and antibiotics were initiated. Despite the escalating antibiotic regimens, the three patients had a persistent high-grade fever. The negative cultures and the continuous fever prompted an investigation for other causes of fever. Therefore, CMV polymerase chain reaction in blood was performed and revealed high titres. Patients received a full course of treatment with ganciclovir. The fever and the CMV titres declined after completing the antiviral therapy with better clinical outcomes. This raises the concern of CMV reactivation in LVAD patients.

## Discussion

This case series and literature review highlight the epidemiology, incidence, and management of CMV reactivation among LVAD patients. Awareness about this clinical entity should be raised, especially with the increase of LVAD surgeries.

## Keywords

Cytomegalovirus • CMV reactivation • Left ventricular assist device • Case report

## Learning points

- Clinicians need to have a low threshold for testing cytomegalovirus (CMV) in left ventricular assist device (LVAD) patients with unexplained fever, or with gastrointestinal bleed.
- Different risk factors can contribute to CMV reactivation in LVAD patients like male gender, positive CMV IgG, prolonged intensive care unit stay, blood transfusion, and severe sepsis.

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## Introduction

Cytomegalovirus (CMV) belongs to the Herpesvirus family. It causes a spectrum of human illnesses in both immunocompromised and immunocompetent. Infection in immunocompetent is mostly asymptomatic. However, it may present as a mononucleosis-like syndrome. Infection in immunocompromised causes significant morbidity and mortality.<sup>1,2</sup> The proportion of humans with evidence of previous CMV infection (seropositive CMV) ranges from 40% to 100%, with the difference between developing and developed countries and between different age groups.<sup>3–5</sup> Reactivation of CMV can occur at any time; however, the risk is higher in the setting of immunosuppression. The immunosuppression can be primary or secondary to underlying medical conditions such as AIDS, haematological malignancies, and glucocorticoid use. Cytomegalovirus reactivation can occur in critically ill non-immunocompromised patients with male gender, positive CMV IgG, prolonged intensive care unit (ICU) stay, blood transfusion, and severe sepsis as risk factors.<sup>6</sup>

Left ventricular assist device (LVAD) is a well-known therapy for advanced systolic heart failure as a destination therapy or as a bridge to heart transplantation. The most common complications post-LVAD placement are device failure, stroke, right-sided heart failure, aortic regurgitation, bleeding, haemolysis, thrombosis, driveline infections, and ventricular arrhythmias.<sup>7,8</sup> Left ventricular assist device patients are at risk for factors that cause CMV reactivation, as prolonged ICU stay, sepsis, and frequent blood transfusions.<sup>9</sup> Here, we present three cases of CMV reactivation in LVAD patients. The possible pathophysiology and the management of CMV reactivation among those patients will be highlighted through a comprehensive literature review of the emerging topic.

## Timeline

## Cases presentation

### Case 1

A 55-year-old male patient known to have rheumatic heart disease had aortic valve replacement twice. He had heart failure with reduced ejection fraction <20%, status post-CRTD, chronic kidney disease with baseline creatinine 1.2–1.5 mg/dL, and atrial fibrillation on warfarin. He presented with terminal cardiac decompensation with cardiorenal syndrome, volume overload, diuretic resistance requiring dialysis, maximal doses of three inotropes, and an intra-aortic balloon pump (IABP) (INTERMACS 1). An urgent high-risk LVAD surgery was performed as a bridge to decision. Heartmate II LVAD was placed. As a part of the pre-LVAD workup, CMV IgG was taken before the LVAD implantation, and it was positive. The patient had fever post-op Day 1. Chest X-ray (CXR) showed pneumonia, and his deep tracheal aspirate (DTA) grew *Escherichia coli* that was sensitive to the meropenem. He completed 10 days of meropenem. Follow-up CXR that showed improvement in the size of alveolar infiltrates with negative DTA culture. Pneumonia resolved, after which the patient was planned for extubation. However, he spiked a high-grade fever post-op Day 11. Pan-cultures were taken, and colistin was added empirically. However, all cultures turned out to be negative. The CXR showed resolving pneumonia. The patient continued to spike fever, so a CMV polymerase chain reaction (PCR) in blood was obtained after 3 days of constant fever (post-op Day 14), and turned out to be positive with very high titres 64 000 copies/mL. The patient was started on ganciclovir 1.25 mg/kg every 48–72 h; then maintenance: 0.625 mg/kg every 48–72 h adjusted based on haemodialysis, and the fever subsided. Follow-up CMV PCR in the blood dropped to 1930 copies/mL 10 days after therapy. This patient developed the CMV reactivation 14 days after LVAD implantation. This patient developed gastrointestinal (GI) bleed on post-op Day 20, and colonoscopy showed healthy mucosa and bleeding haemorrhoids that were ligated. Unfortunately, this patient died after 40 months from the LVAD insertion date. He died from septic shock and acute

	Presentation	Type of the device inserted	Cytomegalovirus (CMV) status before left ventricular assist device (LVAD) implantation	Pneumonia	Symptom of CMV presentation	CMV reactivation	Time to death	Cause of death
Patient 1	Decompensated heart failure (intra-aortic balloon pump (IABP) and Inotropes)	Heartmate II LVAD	IgG positive	Post-op Day 1	Fever post-op Day 11	Post-op Day 14	40 months	Septic shock and acute decompensated heart failure following LVAD dysfunction
Patient 2	Decompensated heart failure (IABP and extracorporeal membrane oxygenation)	Heartmate II LVAD	IgG positive	Post-op Day 3	Fever post-op Day 10	Post-op Day 12	48 months	Died while he was undergoing surgery for aortic valve replacement due to severe aortic insufficiency
Patient 3	Elective presentation for LVAD insertion	Heartmate II LVAD	IgG positive	Post-op Day 2	Fever post-op Day 10	Post-op Day 12	18 months	Disseminated intravascular coagulation

decompensated heart failure following LVAD dysfunction. The cause of death is not related to CMV reactivation.

## Case 2

A 45-year-old male patient, known to have multiple comorbidities, including idiopathic severe dilated cardiomyopathy, severe pulmonary hypertension, dyslipidaemia, hypertension, hyperthyroidism, chronic kidney disease with baseline creatinine 1.2 mg/dL, and atrial fibrillation, presented to the hospital with a picture of heart failure decompensation. He failed medical treatment with inotropes and IABP, bridged by extracorporeal membrane oxygenation to LVAD insertion 3 days later as a bridge to transplantation (INTERMACS I). As a part of the pre-LVAD workup, CMV IgG was taken before the LVAD implantation, and it was positive. Heartmate II LVAD was placed complicated by RV failure, necessitated a short-term RVAD with a Levitronix Centrimag centrifugal pump. The patient spiked a fever post-op Day 3. The CXR showed ventilator-associated pneumonia. He was initially started on piperacillin/tazobactam. Deep tracheal aspirate cultures grew *Acinetobacter*, for which he was switched to colistin post-op Day 5. Initially, the patient improved with no fever until post-op Day 10, when he spiked a high-grade fever. Sepsis workup was done. Meropenem and vancomycin were added to the colistin. His CXR, done post-op Day 12, showed improvement of the previous alveolar infiltrates. The patient continued to have a high-grade fever, so CMV PCR and Epstein–Barr Virus PCR in blood were obtained on post-op Day 12. Cytomegalovirus PCR in blood turned out positive with 940 copies/mL. The patient was started on ganciclovir adjusted to GFR. Follow-up CMV PCR in blood showed undetectable titres after 11 days of treatment. Clinically, he improved progressively with no fever. The patient received 2 weeks of treatment with intravenous (IV) ganciclovir. This patient developed CMV reactivation 10 days after LVAD implantation; however, PCR was taken on Day 12. Unfortunately, this patient died intraop after 48 months from the LVAD insertion date while undergoing aortic valve replacement due to aortic insufficiency. The cause of death is not related to CMV reactivation.

## Case 3

A 57-year-old-male patient known to have coronary artery disease status post-coronary artery bypass graft, complicated by severely dilated end-stage left ventricular dysfunction with ejection fraction <20% status post-CRTD insertion along with severe mitral and tricuspid regurgitation. His right heart function was borderline. He had advanced heart failure stage D INTERMACS 4. He presented electively for LVAD insertion and tricuspid annuloplasty. As a part of the pre-LVAD workup, CMV IgG was taken before the LVAD implantation, and it was positive. The patient developed post-op ventilator-associated pneumonia post-op Day 2 after the insertion of a Heartmate II VAD, for which he was started on meropenem, and levofloxacin was added after the DTA culture grew *Klebsiella pneumoniae* and *Hemophilus influenzae*. The patient remained afebrile for 8 days until, on post-op Day 10, he spiked a fever. Sepsis workup was done. Inhaled Colistin and tigecycline were added, and meropenem was stopped. Cultures were negative, and CXR showed improvement of the previous alveolar infiltrates. However, the patient continued to have fever, so a CMV PCR in blood was obtained post-op Day 12.

Cytomegalovirus PCR in blood came back positive with 939 copies/mL. The patient was started on ganciclovir adjusted to GFR. Follow-up CMV PCR in blood revealed undetectable titres after 14 days of treatment. The patient received 2 weeks of treatment with IV ganciclovir. He developed CMV reactivation 12 days after LVAD implantation. He was positive for CMV IgG prior to the LVAD implantation. Unfortunately, this patient died after 18 months from the date of the LVAD insertion because of disseminated intravascular coagulation upon further admission to the hospital. The cause of death is not related to CMV reactivation.

## Discussion

Continuous flow ventricular support devices known as LVADs are increasingly used for the management of patients with advanced heart failure as destination therapy, bridge to heart transplantation, or bridge to decision or recovery.<sup>10–12</sup> Left ventricular assist devices have been proved to prolong survival and improve heart failure patients' quality of life. However, its insertion is associated with multiple complications. The most common complications are bleeding, infection, pump thrombosis, right-sided heart failure, and device malfunctions.<sup>7,8</sup> Infection is a well-known complication after LVAD implantation. Infection can occur in the pump, in the pump pocket, and around the driveline. Continuous axial flow pumps have smaller surface areas of foreign material and smaller drivelines than the pulsatile pumps and subsequently have lower infection rates.<sup>13</sup> Among the uncommon infections that may occur in LVAD patients is CMV reactivation. Few reports have been documented in the literature about CMV reactivation in LVAD patients.<sup>9,14</sup>

Different theories have been proposed about the cause of CMV reactivation after LVAD implantation. One theory has described aberrant local and systemic effects on host immune responses post-LVAD placement.<sup>15–17</sup> Although most studies were conducted about the pulsatile LVAD pump, similar immune defects may be present with continuous flow pumps. Dysfunctional systemic immune responses appear to be related to interactions between the circulating immune system and the endovascular surface of the device. Left ventricular assist device recipients have shown lower expression of pro-inflammatory cytokines such as interleukin IL-2, TNF-alpha, and higher expression of suppressive IL-10 and T regulatory cells during *in vitro* antigenic challenge, compared with non-LVAD advanced heart failure patients.<sup>17</sup> Abnormal activation of B cells after LVAD implantation has also been described. This may induce autoimmunity and the production of autoantibodies. Yet, the exact pathophysiology of the mechanism of CMV reactivation is not clear. Different risk factors have been contributed to CMV reactivation in non-immunocompromised patients.<sup>6</sup> They are not limited to the male gender, positive CMV IgG, prolonged ICU stay, blood transfusion, and severe sepsis.<sup>6</sup> The different risk factors and the aberrant local and systemic effects on host immune responses after LVAD implantation can help us understand the reason for CMV reactivation in those patients. Our reported three cases were all males, critically ill, septic on antibiotics due to pneumonia, and had received multiple blood transfusions.

Literature about CMV reactivation in LVAD patients is scarce and limited to a few case reports or case series. Lundgren et al.<sup>14</sup>

reported eight patients in a retrospective cohort with a matched control. Six (75%) of the eight patients had CMV viraemia, while the other two had colitis and pneumonia with no evidence of viraemia. The average days from LVAD implantation to CMV viraemia were 47 days. Compared with our case series, five of them had a concurrent bacterial infection, while our three cases had pneumonia before the CMV reactivation. Three of their patients were on corticosteroids, while none of our patients were on corticosteroids. Our patients were sick early in the first 2 weeks, while no details were found regarding the early status of their patients. Despite the small sample size of this retrospective cohort, it raises the concern of the previously proposed risk factors. Thangam *et al.*<sup>18</sup> reported a case of CMV viraemia and CMV retinitis after Tandem-Heart was implanted in a severely sick patient with prolonged hospital stay but with no previous immunosuppression. In this reported case, the patient was septic immediately after the LVAD insertion like our patients; however, he developed the CMV reactivation after 48 days.

Sandkovsky *et al.*<sup>9</sup> reported two cases of GI bleed due to CMV reactivation post-LVAD implantation, and only one of them had CMV viraemia. Both cases were successfully treated with ganciclovir. The first case had GI bleed reported post-op Day 20, while the other one had GI bleed that required medical management before proceeding with haemicolectomy, after which the biopsy showed CMV colitis. The reported date of CMV reactivation was when the biopsy was taken during surgery, while the GI bleed happened days before. Huttner *et al.*<sup>19</sup> reported one case of CMV pneumonitis and ileitis based on post-mortem biopsies and pleural fluid samples collected before death, 53 days after LVAD implantation. Pathology from the lung showed necrotizing pneumonia, inclusion bodies, and positive CMV stains. Pathology from the ileum showed ileitis with positive CMV stains, and pleural fluid showed positive CMV PCR. This patient was very sick and was in septic shock after LVAD implantation and passed away during this hospital admission. Aleksic *et al.*<sup>20</sup> reported a case of CMV ileitis/enteritis, 27 days post-LVAD with no initial serology or PCR was done. However, pathology showed ileitis and positive CMV stains. This patient was very sick immediately after LVAD insertion, shocked, and in respiratory failure with a long hospital stay of 90 days. Pfau and Rothstein<sup>21</sup> reported a case of lower GI bleeding and caecal ulcer. Pathology of the caecal ulcer showed acute inflammatory exudate and intranuclear inclusion suggestive of CMV colitis. GI bleed was a major clinical presentation in these patients, and in these cases, colectomy was the treatment of choice. In our case series, Case 1 had GI bleed, and colon biopsy did not detect CMV infection and was due to bleeding haemorrhoids. All three cases were treated with IV ganciclovir.

Our case series showed that reactivation could occur earlier, between 12 and 14 days post-LVAD implantation, while most of the cases reported in literature observed reactivation after at least 25 days of LVAD insertion. Limaye *et al.*<sup>22</sup> reported in their prospective trial about CMV reactivation in critically ill immunocompetent patients that CMV reactivation occurs at a median of 12 days, which is around the same time as our patients. Our early testing for CMV matches the findings in this prospective trial. All our patients were HIV negative, and none of them were on any corticosteroids or other immunosuppressive treatment. None of them had lymphadenopathy, atypical lymphocytes, or symptoms suggestive of CMV reactivation

other than the persistence of fever. Our medical team decided to get CMV PCR because of the continuous fever despite starting antibiotics and the negative cultures based on our centre clinical experience. Cytomegalovirus reactivation did not affect our patients' mortality as the cause of death was not linked to the CMV reactivation. Yet, our early diagnosis led to this better outcome.

In all the case reports and series in the literature, nearly all patients had risk factors for CMV reactivation after LVAD implantation. However, data are very limited with the small number of reported cases and only one retrospective study that included only eight patients. No adjustment for different risk factors was made, and no comparison arms were done as well except for Lundgren *et al.* Further clinical studies are recommended, including multicentre studies for a better understanding of this clinical presentation. Clinicians need to have a low threshold for testing for CMV in LVAD patients with unexplained fever and with GI bleed.

## Lead author biography



Dr Hadi Skouri is an associate professor of Clinical Medicine-Cardiology and a Heart Failure specialist. He is the Director of the Cardiac Failure Unit and the Heart Failure Programme at AUBMC as well as the co-chairman of the heart failure working group at the Lebanese Society of Cardiology (LSC). He completed a 2-year fellowship in heart failure and transplantation at Mayo Clinic-Rochester, and Cleveland Clinic Foundation. He is key member of several Heart Failure Association of the European Society

of Cardiology committees including the Acute and Advanced Heart failure committee and the National Heart Failure Societies committee at the Heart Failure Association of the European Society of Cardiology. He has written more than 40 published papers.

## Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

**Slide sets:** A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

**Consent:** The patients reported in this case series are unfortunately deceased. Despite the best efforts of the authors, it has not been possible to contact the next of kin. All efforts have been made to anonymise the cases. This has been discussed and agreed with the editors.

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