Cambridge City Publishers

Case Reports in Clinical Cardiology Journal

Case Report | Vol 4 Iss 1

Recurrence of Giant Cell Myocarditis in a Heart Transplanted Patient with Multiple Autoimmune Diseases

Helga Rún Garðarsdóttir[2*], Ida Löfman[1,2], Magnus Dalén[3,4] and Emil Najjar[1,2]

[1]Department of Medicine, Karolinska Institutet, Stockholm, Sweden

[2]Heart and Vascular Theme, Karolinska University Hospital, Stockholm, Sweden

[3]Department of Cardiothoracic Surgery, Karolinska University Hospital, Stockholm, Sweden

[4]Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden

[*]**Corresponding author:** Helga Rún Garðarsdóttir, Heart and Vascular Theme, Karolinska University Hospital, Stockholm, Sweden. E-mail: helga.gararsdottir@regionstockholm.se

Received: January 28, 2024; **Accepted:** February 17, 2024; **Published:** February 25, 2024

Abstract

Giant cell myocarditis is a rare and frequently fatal inflammatory disorder of unknown origin. We describe a case of a 23-year-old woman with multiple autoimmune diseases who presented with progressive heart failure due to giant cell myocarditis leading to implantation of left ventricular assist device as a bridge to orthotopic heart transplantation. During follow-up, endomyocardial biopsy has twice shown reappearance of giant cells in the transplanted heart allograft.

Keywords: Giant cell myocarditis; Fulminant myocarditis; Left ventricular assist device; Orthotopic heart transplantation

Abbreviations

CCU: Cardiac care unit; EMB: Endomyocardial biopsy; GCM: Giant cell myocarditis; ICU: Intensive care unit; LVEF: Left ventricular ejection fraction; LVAD: Left ventricular assist device; OHT: Orthotopic heart transplantation; TTE: Transthoracic echocardiography; VA-ECMO: Venoarterial extracorporeal membrane oxygenation

Introduction

Giant cell myocarditis (GCM) is a rare but aggressive myocardial disease of unknown origin [1]. It is characterized by diffuse myocardial necrosis and infiltration of T lymphocytes with multinucleated giant cells [2]. The main medical treatment is immunosuppressants and guideline-directed heart failure medication but this is rarely successful. The patient may suffer from progressive severe heart failure with need of heart transplantation [3]. We describe the clinical course of a young woman with GCM who presented with cardiogenic shock and was treated with venoarterial extracorporeal membrane oxygenation (VA-ECMO), left ventricular assist device (LVAD), and finally underwent orthotopic heart transplantation (OHT). There was a recurrence of GCM in the cardiac allograft concurrently with rejection.

Case Presentation

A 23 year old woman with a past medical history of ulcerative colitis, autoimmune pancreatitis, and psoriasis presented to our emergency department with chest pain and progressive dyspnea. On examination her vital signs were as follows: temperature, 37°C; blood pressure, 114/81 mmHg; heart rate, 119 bpm; SpO2, 96% on room air; and respiratory rate 25 breaths/min. Heart and lung examination was normal. Electrocardiogram demonstrated sinus tachycardia with ST-elevation in leads V1-V3 and ST-depression in leads V5-6, and I (Figure 1). Laboratory blood tests showed evidence of myocardial injury (troponin t: 1190 ng/L and NT-proBNP: 15400 ng/L) and systemic inflammation (CRP: 57 mg/L). Computed tomography pulmonary angiogram showed no signs of pulmonary embolism and coronary angiography was normal. Transthoracic echocardiogram (TTE) showed normal left ventricular dimensions with reduced ejection fraction (LVEF) of 30%, akinesia in apical segments, a reduced right ventricular function and no significant valve disease.

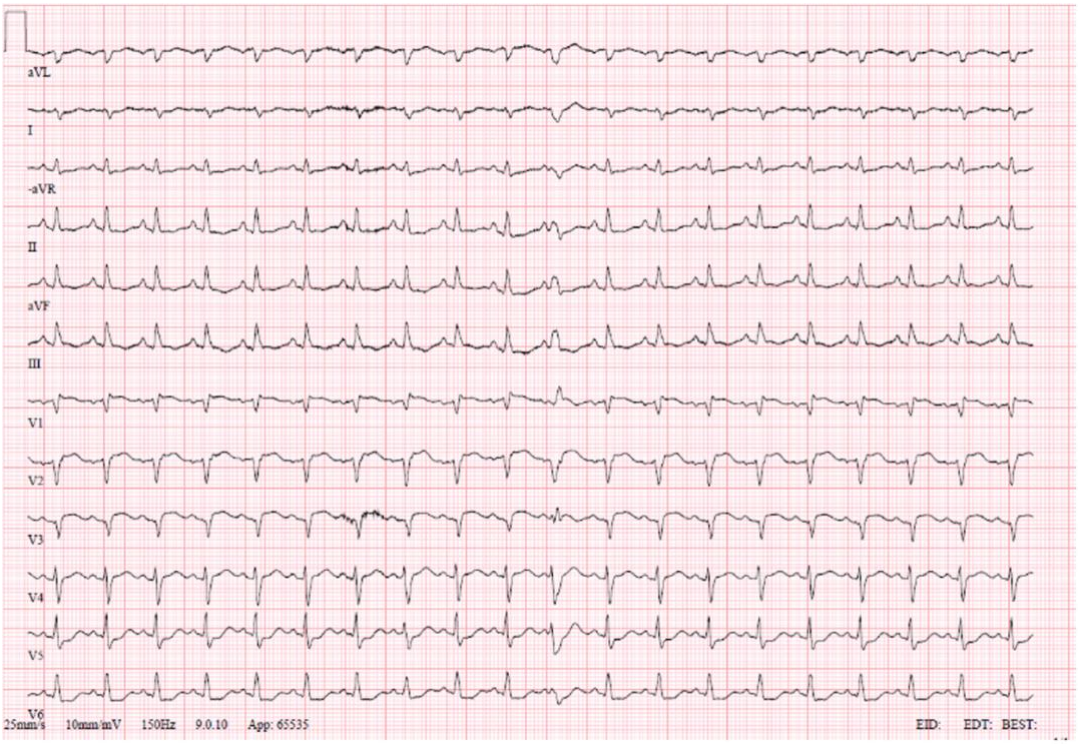

Figure 1: Electrocardiogram at admission showing sinus tachycardia. ST-elevation in leads V1-V3 and ST-depression in leads V5-6, and I.

Fourteen hours after admission the patient developed hypotension (BP 81/66 mmHg) with hypoperfusion, requiring vasopressor support and was admitted to the intensive care unit (ICU). Despite increased IV noradrenalin, and infusion with two inotropic agents; levosimendan and milrinone, she continued to deteriorate. Endomyocardial biopsy (EMB) on day 2 demonstrated destructive myocarditis with infiltration of lymphocytes and eosinophils with giant cells. Immunosuppressive therapy was started with IV methylprednisolone 500g and Mycophenolate mofetil 1g x 2 and pre-transplant workup was initiated. Despite treatment the patient´s condition deteriorated and the decision was made on day 4 to initiate VA-ECMO (venoarterial extracorporeal membrane oxygenation). The following day tacrolimus was added for more aggressive immunosuppression.

The patient stabilized and improved over the next days, and a repeat EMB demonstrated no eosinophils and no giant cells. She was weaned off VA-ECMO after 16 days, and the following day moved back to the CCU. Cardiac magnetic resonance imaging on day 28 showed a dilated left ventricle with transmural fibrosis, very thin septum of 2 mm, LVEF of 25% with subepicardial and transmural scarring indicative of GCM (Figure 2). After 55 days of hospital stay she was discharged home. Prior to discharge she received an implantable cardioverter defibrillator (ICD). Despite repeated levosimendan infusions and IV diuretics the hypotension persisted, requiring a decrease in heart failure medication. After complete pre-transplant work-up she was accepted to the heart transplantation waiting list.

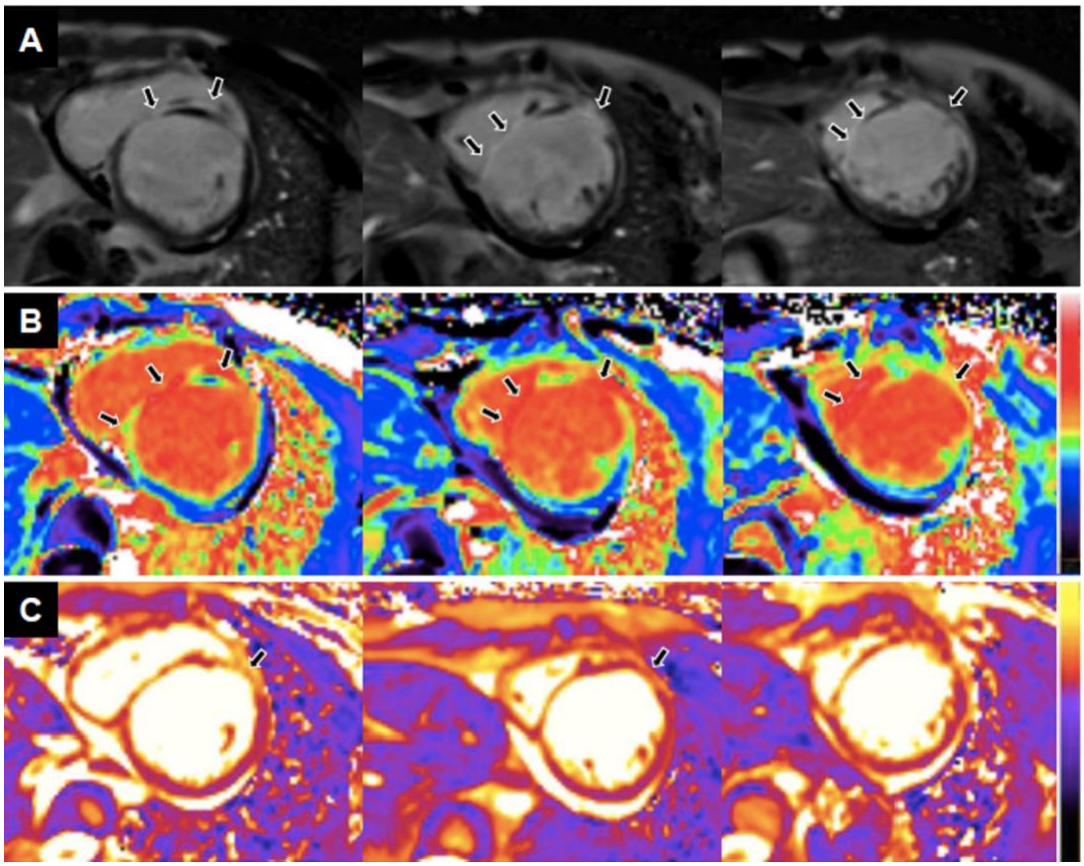

Figure 2: Cardiac magnetic resonance imaging. **(A):** Late Gadolinium Enhancement (LGE) short-axis images showing subepicardial and transmural scaring in the basal to mid interventricular septum and transmural and subendocardial in the mid and apical anterior wall (arrows); **(B):** Extracellular volume (ECV) maps and **(C):** T2 maps of corresponding stacks showing increased ECV and T2 values in the septum and anterior wall (arrows). Figures from Dr. Göran Abdullah, Clinical physiology, Region Stockholm.

Six months after discharge her condition deteriorated again with hypotension and worsening kidney function. TTE showed LVEF 15-20% and right ventricular systolic dysfunction and high systolic right ventricular pressure 55 mmHg (Figure 3). She was admitted to the ICU with inotrope support and continuous renal replacement therapy. Right catheterization showed high mean pulmonary artery pressure (30 mmHg) and high pulmonary capillary wedge pressure (22 mmHg) with low cardiac index (1,95 L/min/m^2).

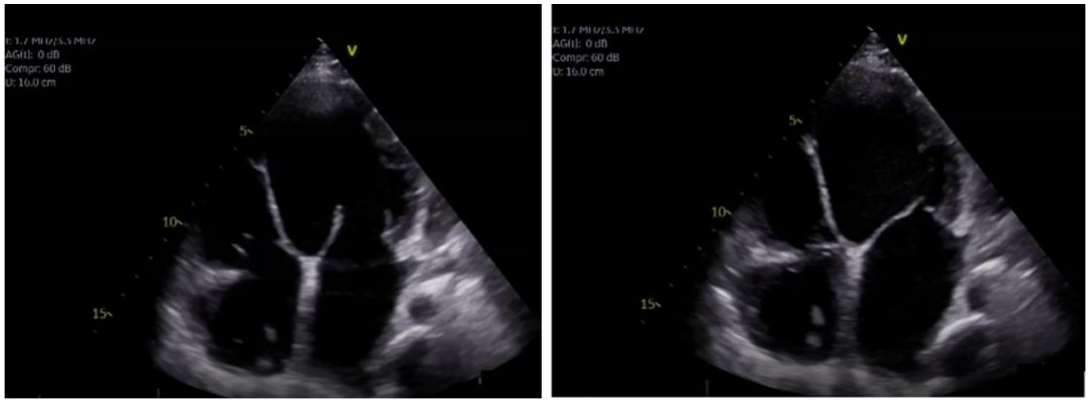

Figure 3: Transthoracic echocardiogram four-chamber view six months after discharge (end-diastolic image on the left, end-systolic image on the right) demonstrating dilated left ventricle with severly impaired ejection fraction and very thin interventricular septum (3 mm).

Thus, the decision was made to proceed with a Heartmate3© left ventricular assist device (LVAD) as a bridge to heart transplantation. Immunosuppressive treatment other than prednisolone was stopped before LVAD implantation due to poor kidney function. Her condition was stable the first three weeks post LVAD implantation but then she started to have low flow alarms. TTE showed signs of right heart failure which was managed by LVAD speed optimization, adjustment of diuretic dose, the use of levosimendan, and sildenafil was added.

Two months after LVAD implantation she was again admitted to the ICU, this time because of ventricular arrhythmias and repeated shocks from the ICD. TTE showed EF 5% and severe right ventricular dysfunction and a decision was made to restart immunosuppresive treatment with methylprednisolone, tacrolimus, and mycophenolate and initiate VA-ECMO. She was accepted for urgent heart transplantation and received a matched heart the following day. Histopathological examination of the explanted heart demonstrated fulminant giant cell myocarditis (Figure 4). IV anti-thymocyte globulin 50 mg was given directly after OHT in addition to the traditional heart transplant immunosuppression regime.

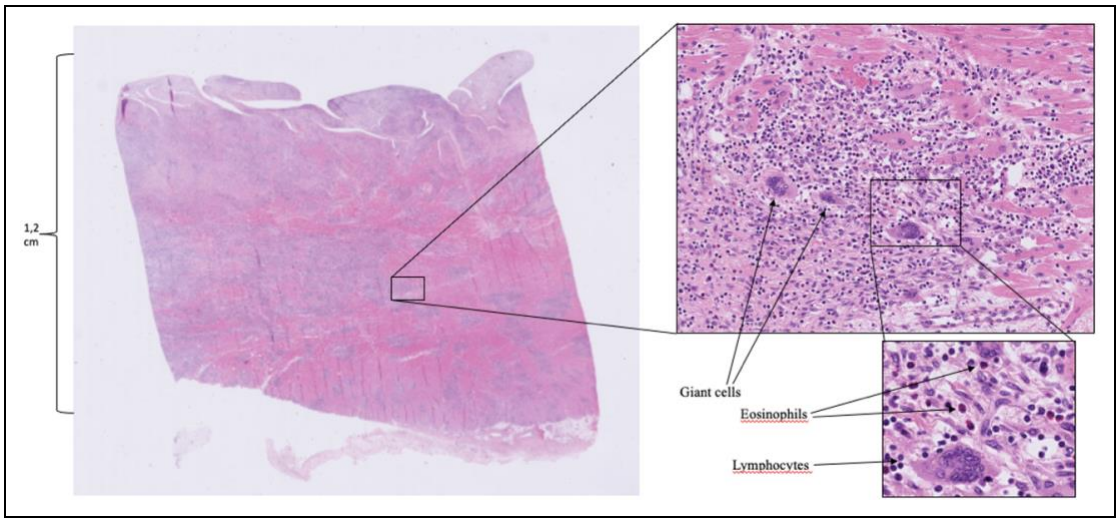

Figure 4: Endomyocardial biopsy from the explanted heart. Cardiomyocytes largely replaced by severe chronic inflammation with eosinophils and multinucleated giant cells. Figures from Dr. Kaja Ericson Lindquist, Clinical pathology, Region Skåne.

Three months after heart transplantation, a scheduled EMB showed signs of G2R rejection and she was treated successfully with intravenous methylprednisolone. However, three months later the EMB showed again G2R rejection and reappearance of giant cells indicative of GCM in the transplanted heart allograft. She was treated with methylprednisolone intravenously, the dose of tacrolimus was increased and thymoglobuline 1,5 mg/kg was added for 4 days. EMB one month later showed no signs of GCM or rejection. EMB 9 months after OHT showed again reapperance of GCM, which was treated with IV Rituximab 60 mg. To date, 18 months after OHT, she has not experienced further G2R rejection or reactivation of giant cell myocarditis in the transplanted heart.

Discussion

Patients with GCM most commonly present with rapidly progressive heart failure [1]. Therefore, the first treatment focus is on heart failure medication. After confirmed diagnosis, immunosuppressive therapy is the main medical treatment for GCM [1,2] but due to the rarity of the disease the optimal treatment and duration is not known, and often delayed. To date, the immunosuppresive regimen is usually based on triple therapy with a calcineurin inhibitor, an antimetabolite and glucocorticosteroids. Studies have shown that aggressive immunosuppressive treatment can improve survival and postpone or even avoid the need for mechanical circulatory support and heart transplantation [1].

Our patient needed VA-ECMO support for stabilisation before further treatment decision and was successfully weaned. Studies on appropriate choice of short-term mechanial support are lacking but usully VA-ECMO is used [3]. However, the use of VA-ECMO increases afterload which may exacerbate myocardial wall stress and promote inflammation. A possible alternative or addition to unload the left ventricle is the percutaneous intraventricular axial flow pump (Impella) [4].

After LVAD implantation, the immunosuppresive therapy, other than corticosteroids, was discontinued because EMB showed only fibrosis and no signs of inflammation. Examination of the explanted heart showed fulminant GCM. One may consider to continue the immunosuppressive therapy after LVAD implantation to decrease the risk of GCM recurrence. On the other hand, immunosuppresive therapy increases the risk of infections, such as drive line infections [5]. GCM often presents in patients with underlying autoimmune diseases which probably indicate a overly active immune system. It should be taken into consideration that these patients need more aggressive immunosuppressive treatment. A recent study proposed increased survival with use of intravenous anti-thymocyte globulin during the perioperative period and early initiation of potent immunosuppresive therapy including tacrolimus [6].

The risk of recurrence of GCM in heart allografts has been described in up to 25% of patients [7] but it tends to be more benign than GCM in the native heart and this high prevalence should not be considered as a barrier for OHT [8]. It is important to continue immunosuppressive therapy long-term after OHT because the risk for recurrence have been found to persist for up to 8 years if the treatment is tapered or discontinued [9]. There is also evidence of a higher incidence of recurrence if LVAD is used as a bridge to transplantation, the reason for this is unknown. This finding could be biased by the fact that patients with

more severe GCM are selected for LVAD bridge to transplant [10]. However, LVAD also increases health status of patients planned for OHT by improving functional capacity and quality of life [11]. To date, there are no prospective trials that demonstrate optimal treatment for GCM recurrence.

Owing to the rarity of this disease, evidence based guidelines are lacking and the recommendations available are based on expert consensus, single center experiences and pooled analysis from multiple centra. With aggressive immunosuppressive treatment and early diagnosis the dismal prognosis can be significantly improved. Further studies are required to define the optimal treatment of patients with GCM.

Conclusion

GCM is a rare but severe disease that warrants high suspicion. This case is not unique but illustrates the importance of maintaining immunosuppression throughout the treatment because of the aggressive nature of the underlying disease. This case shows the importance of multidisciplinary team approach due to the complexity of the disease.

Learning Objectives

- To recognize that myocarditis can be a challenging diagnosis and high degree of suspicion is required.
- To highlight the complexity of Giant cell myocarditis treatment and the importance of multidisciplinary team approach.

REFERENCES

1. Cooper LTJ, Berry GJ, Shabetai R. Idiopathic giant-cell myocarditis-natural history and treatment. Multicenter Giant Cell Myocarditis Study Group Investigators. N Engl J Med. 1997; 336: 1860-1866.
2. Cooper LT, Hare JM. Usefulness of Immunosuppression for Giant Cell Myocarditis. Am J Cardiol. 2008.
3. Den Uil CA, Akin S, Jewbali LS, et al. Short-term mechanical circulatory support as a bridge to durable left ventricular assist device implantation in refractory cardiogenic shock: A systematic review and meta-analysis. European Journal of Cardio-thoracic Surgery. 2017.
4. Tschöpe C, Van Linthout S, Klein O, et al. Mechanical Unloading by Fulminant Myocarditis: LV-IMPELLA, ECMELLA, BI-PELLA, and PROPELLA Concepts. J Cardiovasc Transl Res. 2019.
5. Siméon S, Flécher E, Revest M, et al. Left ventricular assist device-related infections: a multicentric study. Clin Microbiol Infect. 2017.
6. Vaidya GN, Czer LSC, Luthringer D, et al. Heart Transplantation for Giant Cell Myocarditis: A Case Series. Transplant Proc. 2021.
7. Cooper LT. Giant cell myocarditis: Diagnosis and treatment. Herz. 2000.
8. Scott RL, Ratliff NB. Recurrence of giant cell myocarditis in cardiac allograft. J Hear Lung Transplant. 2001.
9. Maleszewski JJ, Orellana VM, Hodge DO, et al. Long-Term Risk of Recurrence, Morbidity and Mortality in Giant Cell Myocarditis. Am J Cardiol. 2015.
10. Brilakis ES, Olson LJ, Berry GJ, et al. Survival outcomes of patients with giant cell myocarditis bridged by ventricular assist devices. ASAIO J. 2000.
11. Miller LW, Pagani FD, Russell SD, et al. Use of a Continuous-Flow Device in Patients Awaiting Heart Transplantation. N Engl J Med. 2007.