

# Case report of heart transplantation for giant cell myocarditis in a patient with common variable immunodeficiency

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Received 15 April 2021; first decision 3 June 2021; accepted 4 November 2021; online publish-ahead-of-print 18 November 2021

## Background

Solid-organ transplantation in patients with common variable immunodeficiency (CVID) is controversial due to the risk for severe and recurrent infections. Determining transplantation candidacy in CVID patients is further complicated by the presence of CVID-related non-infectious complications that can reduce overall survival and also recur in the transplanted organ. Data regarding solid organ transplantation in patients with CVID are limited, particularly in heart transplantation.

## Case summary

A 32-year-old female with CVID presented with new heart failure after 3 months of dyspnoea on exertion. Her echocardiogram showed severe global systolic dysfunction with an ejection fraction of approximately 10%, and her right heart catheterization revealed severe biventricular pressure overload and severely reduced cardiac output. Endomyocardial biopsy revealed giant cells and mononuclear infiltrate consistent with giant cell myocarditis (GCM). Despite medical management, she developed progressive cardiogenic shock and underwent uncomplicated orthotopic heart transplantation on hospital Day 38. After 2 years of follow-up, she has had no major infectious complications and continues to have normal graft function with no recurrence of GCM.

## Conclusion

We report a case of successful heart transplantation for GCM in a patient with CVID, with no major infectious complications after 2 years of follow-up. CVID should not be considered an absolute contraindication for heart transplantation.

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Handling Editor: Erik Holy

Peer-reviewers: Josip Andelo Borovac and Rafael Vidal-Perez

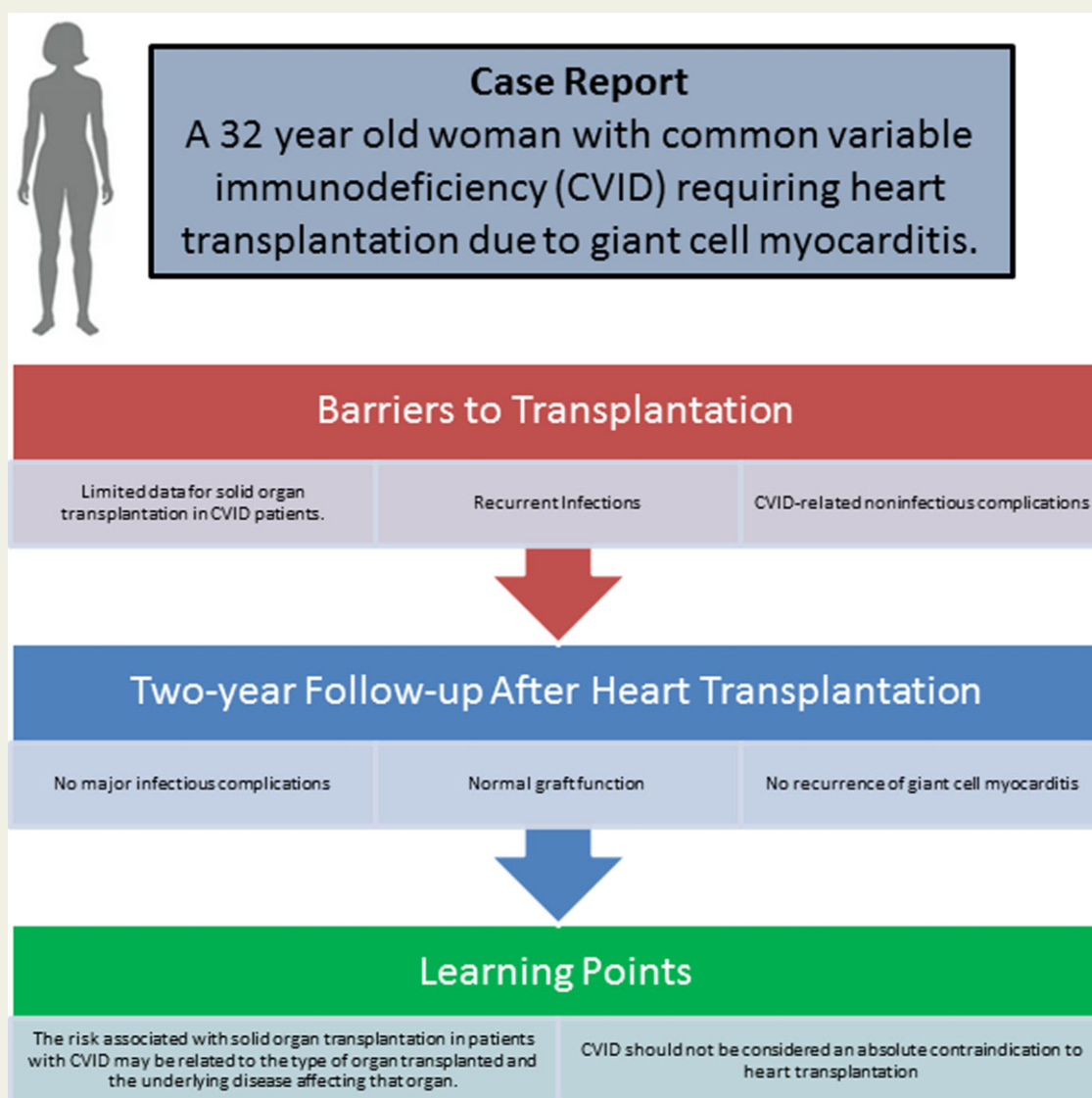
Compliance Editor: Kajaluxy Ananthan

Supplementary Material Editor: Ross Thomson

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## Graphical Abstract



### Keywords

Heart transplant • Acute heart failure • Cardiomyopathy • Common variable immunodeficiency • Case report

### ESC Curriculum

7.5 Cardiac surgery • 7.3 Critically ill cardiac patient • 7.1 Haemodynamic instability • 6.4 Acute heart failure

### Learning points

- Common variable immunodeficiency (CVID) patients have an increased risk for infectious and non-infectious complications; however, this report suggests that CVID should not be considered an absolute contraindication to heart transplantation.
- The risk associated with solid organ transplantation in patients with CVID may be related to the type of organ transplanted and the underlying disease affecting that organ.
- Giant cell myocarditis is a rare cause of acute decompensated heart failure that often requires heart transplantation.

## Primary specialties involved other than cardiology

Allergy and Immunology, Internal Medicine Anatomic Pathology

## Introduction

Common variable immunodeficiency is considered the most common form of primary immunodeficiency and is characterized by recurrent infections, non-infectious complications, hypogammaglobulinaemia, poor antibody response to vaccines, and the absence of a defined secondary cause of hypogammaglobulinaemia. Immuno-globulin therapy significantly reduces the risk of infection in CVID patients and improves their survival to that of age-matched controls; however, certain non-infectious complications have been shown to increase mortality.<sup>1,2</sup>

Due to the risk for recurrent infection, particularly in the setting of post-transplant immunosuppression, and the concern for non-infectious complications to negatively impact survival, solid organ transplantation in patients with CVID has been controversial. Currently, there are no guidelines that address solid organ transplantation in patients with CVID.

## Timeline

3 months prior to presentation	Dyspnoea and chest tightness on exertion.
Day 1	Presented to our emergency room for evaluation. Troponin mildly elevated and B-type natriuretic peptide significantly elevated. Echocardiography revealed severe left ventricular dysfunction and right heart catheterization revealed severely reduced cardiac output. Started on milrinone and nitroprusside with improvement in haemodynamics. Differential diagnosis included viral myocarditis, eosinophilic myocarditis, giant cell myocarditis (GCM), and autoimmune myocarditis.
Day 5	Endomyocardial biopsy was consistent with GCM.
Day 16	Listed for heart transplant due to persistent low-output heart failure requiring milrinone.
Day 31	Progressive diuretic resistance and persistent cardiogenic shock despite higher doses of milrinone prompted insertion of an intra-aortic balloon pump.
Day 38	Underwent orthotopic heart transplant.

## Case presentation

A 32-year-old female with a history of common variable immunodeficiency (CVID) was admitted to our hospital because of new heart

failure. In the 3 months leading to her presentation, she developed mild dyspnoea and chest tightness on exertion. She had no preceding viral illness.

In the emergency department, her blood pressure was 121/86 mmHg, heart rate 128 beats per minute, respiratory rate 16 breaths per minute, oxygen saturation 98% while breathing room air, and temperature 36.7°C. Examination was notable for jugular venous distension and an S3 gallop. Troponin I was 0.86 ng/mL, B-type natriuretic peptide 1811 pg/mL, venous lactate 3.9 mmol/L, and estimated glomerular filtration rate was >60 mL/min. Chest radiography showed mild cardiomegaly and mild enlargement of the hilar pulmonary vessels. Electrocardiogram showed sinus tachycardia and ST elevations V2–V4, and transthoracic echocardiography revealed a dilated left ventricle with an ejection fraction of approximately 10% (Figure 1). Left heart catheterization revealed normal coronary arteries. Pulmonary artery catheterization revealed a right atrial pressure of 18 mmHg, pulmonary artery pressure of 51/35 mmHg, pulmonary capillary wedge pressure of 30 mmHg, and cardiac index of 1.34 L/min/m<sup>2</sup> by thermodilution.

As a child, she experienced frequent lower respiratory tract infections. She was diagnosed with CVID at age 21 after she was found to have low levels of immunoglobulin (At the time of diagnosis, immunoglobulin levels were IgA 15 (40–350 mg/dL) and IgM 68 (50–370 mg/dL). Baseline IgG was not available from the outside hospital laboratory. Subsequent immunoglobulin levels obtained after diagnosis in the setting of subtherapeutic subcutaneous immunoglobulin replacement were IgA 7, IgM 11, and IgG 146 (620–1520 mg/dL), low titre response to vaccinations, and bronchiectasis on chest imaging. She was started on subcutaneous immunoglobulin and experienced a significant reduction in infections. Also in her 20's, she developed proximal muscle pain and weakness, and chronic watery diarrhoea. Muscle and gastrointestinal biopsies diagnosed polymyositis and collagenous colitis, respectively.

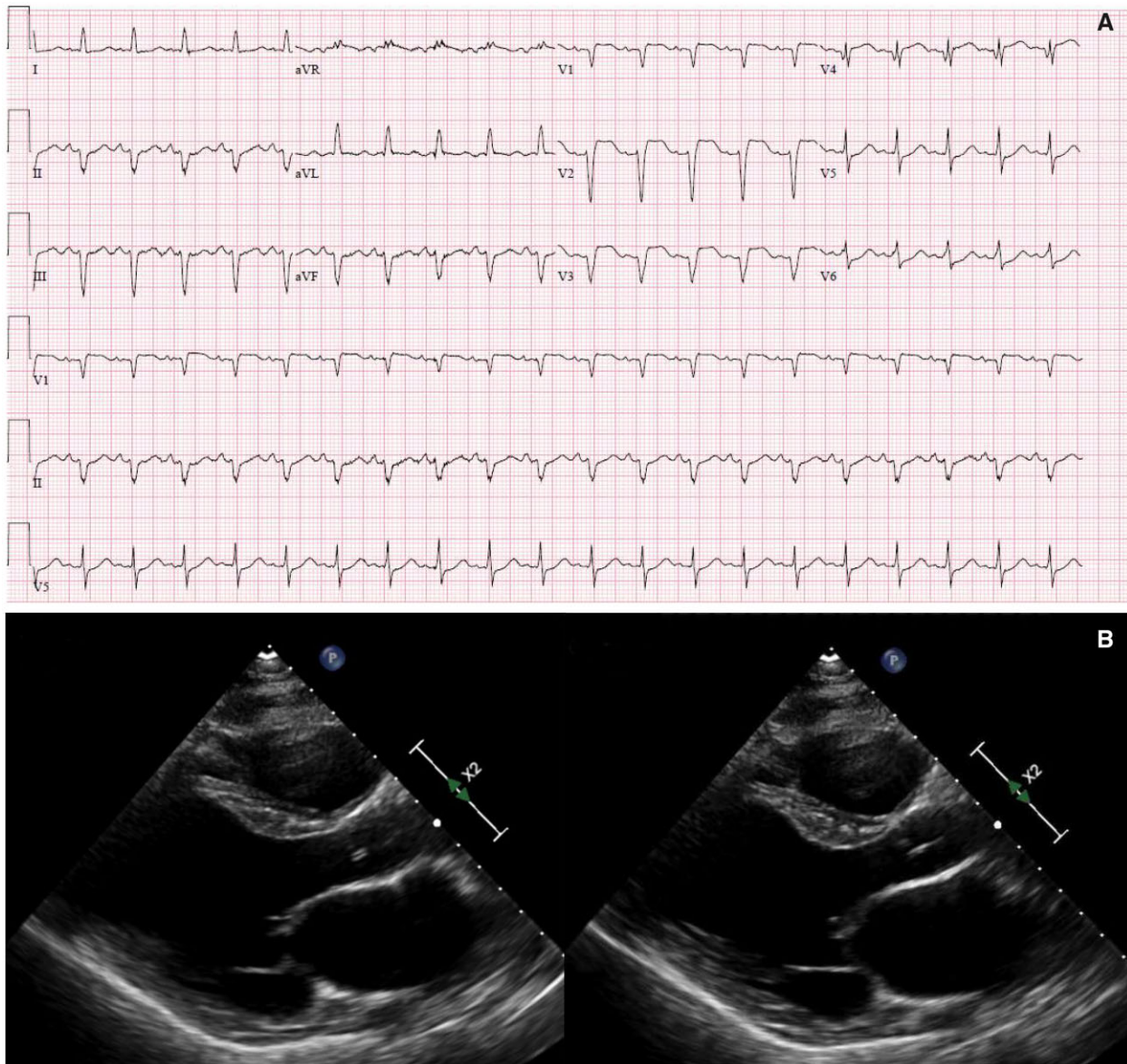
Endomyocardial biopsy showed endocardial and focal perivascular interstitial mononuclear inflammation. Giant cells in addition to mononuclear infiltrate and myocyte drop out were identified, consistent with giant cell myocarditis (GCM) (Figure 2A).

She was initiated on milrinone and nitroprusside with an improvement in her cardiac index to 2.16 L/min/m<sup>2</sup>.

By hospital Day 31, she had developed progressive diuretic resistance and repeat pulmonary artery catheterization revealed a cardiac index of 1.5 L/min/m<sup>2</sup>, which remained low despite higher doses of milrinone, and an intra-aortic balloon pump was inserted.

She underwent an uncomplicated orthotopic heart transplant on hospital Day 38. The explanted heart was notable for a moderately dilated left ventricle (Figure 2B). Post-transplant, she received an immunosuppression regimen of mycophenolate mofetil, prednisone, and tacrolimus. She was discharged on hospital Day 62.

Two years after her transplant, she continued to feel well with no evidence of recurrent GCM, normal graft function, and no serious infectious complications. Minor infectious complications did occur, all of which were treated successfully, including a rectal abscess, treated with oral antibiotics and incision and drainage, oesophageal candidiasis, treated with fluconazole, and CMV viraemia, treated with valganciclovir. She received standard doses of tacrolimus and prednisone



**Figure 1** Electrocardiogram and echocardiogram on admission. An electrocardiogram (A) showed sinus tachycardia, left-axis deviation, ST elevations V2–V4, and poor R-wave progression. Parasternal long axis images of the echocardiogram (B) are shown in end diastole (left) and end systole (right). The left ventricular internal diameter during diastole was 60 mm.

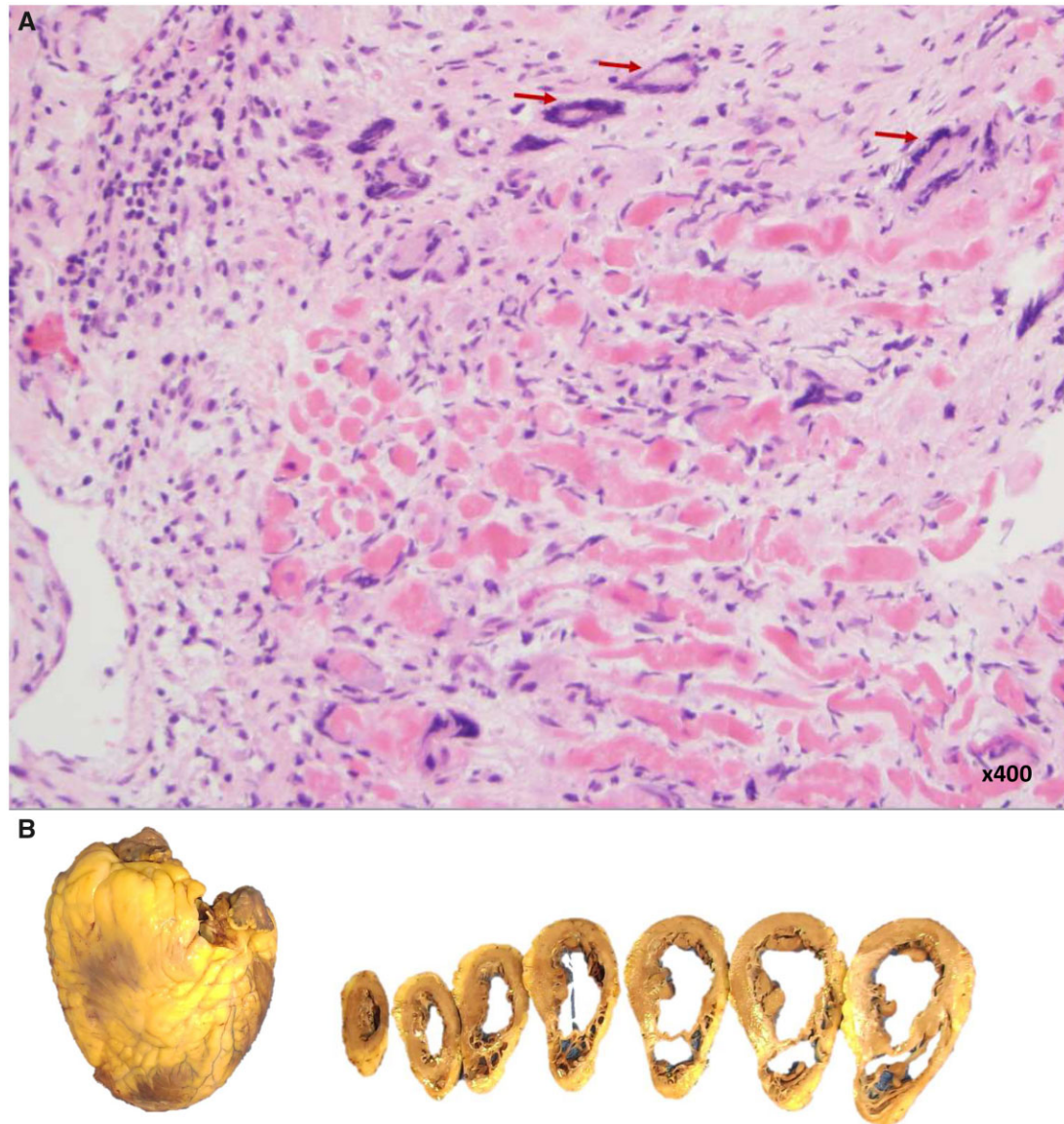
throughout her follow-up; however, her mycophenolate mofetil dose was reduced in consideration of her CVID and minor infections. She had one episode of Grade II cellular rejection 11 weeks after her transplant, which resolved after a temporary increase in mycophenolate mofetil. Due to ongoing symptoms from polymyositis, she continued low-dose prednisone, which otherwise would have been discontinued, as biopsies showed no evidence of rejection. She continued weekly subcutaneous immunoglobulin injections with additional doses as needed to maintain therapeutic immunoglobulin levels, which were measured monthly initially, and then every 3–6 months after a stable regimen was established.

## Discussion

We report a case of successful heart transplantation for GCM in a patient with pre-existing common variable immunodeficiency disorder (CVID), with no major infectious complications after 2 years of follow-up.

The true prevalence of CVID is uncertain due to underreporting and difficulties in diagnosis; however, it has been estimated to be between 1:100 000 and 1:10 000, with a reduced overall median survival of approximately 43 years, ranging from 9 to 90 years.<sup>1</sup>

Reduced survival has been shown to be largely dependent on the presence of non-infectious complications with patients having



**Figure 2** Endomyocardial biopsy and gross images of the explanted heart. Haematoxylin and eosin stain of the endomyocardial biopsy (A) at  $\times 400$  magnification showed interstitial mononuclear inflammation with scattered giant cells (arrows) and myocyte loss. Cross-sections of the explanted heart (B) revealed a moderately dilated left ventricle.

infections as their only manifestation of the disease enjoying similar survival to age-matched controls. In a North American study of 411 CVID patients followed for 40 years, the risk of death was nearly 11 times higher for CVID patients with one or more non-infectious complications, which included gastrointestinal disease, liver diseases and hepatitis, lymphoma, chronic lung disease, and malabsorption.<sup>1</sup> In a similar European study of 334 patients, enteropathy, polyclonal lymphocytic infiltrative disease, lymphoma, and autoimmunity were associated with reduced survival.<sup>2</sup>

Many of these non-infectious phenotypes represent a group of heterogeneous diseases themselves, thus it can be difficult to infer

individual prognosis from these studies. Despite reduced survival in CVID patients with certain non-infectious complications, the median survival of these patients exceeds the median survival of heart transplant recipients.

The increased risk for infection is also of practical concern when considering organ transplantation in CVID patients, given that infection is one of the leading causes of death in heart, liver, kidney, and lung transplant recipients. Predictably, CVID has been cited as a reason to turn down or delay organ transplantation.<sup>3,4</sup>

Data regarding the safety of heart transplantation in patients with CVID are sparse. There has been one documented case of heart

transplantation for GCM in a 12-year-old girl with CVID; however, her post-transplant course beyond hospital discharge is not documented.<sup>5</sup>

A number of case reports have been published describing liver transplantation; however, these patients are susceptible to recurrent CVID-related liver disease, making it difficult to extrapolate their experience to heart transplant recipients, as there are no known CVID-related heart diseases.<sup>6–14</sup> Similarly, case reports of lung transplantation have had mixed results, with severe post-operative lung infections and presumed recurrent CVID-related lung disease complicating some cases.<sup>3,15–18</sup> There are few case reports of renal transplantation in patients with CVID; however, Lund et al.<sup>19</sup> reported three patients with hypogammaglobulinaemia who underwent the renal transplant and had no severe infections with functioning graft after a mean follow-up period of 3.6 years (it was unknown whether these patients had CVID or a secondary cause of hypogammaglobulinaemia). A case report of renal transplantation in a patient with CVID reported acute graft rejection in the setting of medication non-compliance but did not report any infections in the 32-month follow-up period.<sup>20</sup>

Although the number of reported patients with CVID receiving solid organ transplantation is small, these reports suggest that the risk of complications after transplantation may be dependent on which organ is transplanted and the underlying disease affecting that organ.

Our patient presented with acute heart failure secondary to GCM, which in the context of her CVID, created additional management considerations. Giant cell myocarditis is a rare and often fatal form of myocarditis that typically presents between the ages of 30–60 years with a female preponderance. Classic features of GCM include ventricular arrhythmias, high-grade conduction block, and fulminant heart failure. The clinical presentation can mimic acute myocardial infarction, as was seen in our patient.

The most promising medical therapy for GCM has been shown to involve combinations of immunosuppression including cyclosporine; however, transplant-free survival with these regimens is still guarded (69% at 1 year, 58% at 2 years, and 52% at 5 years).<sup>21</sup> Thus, offering medical therapy for GCM in a patient with CVID presents a dilemma in that immunosuppression is both relatively ineffective and increases the risk of infection in an already immunocompromised patient. Although GCM has been shown to recur in transplanted hearts, it often does not recur with the same fulminant presentation, perhaps because of ongoing post-transplant immunosuppression.<sup>21,22</sup> With these considerations, it was felt that the best course of action was to offer our patient heart transplantation.

This report describes the second known heart transplant in a patient with CVID and is the first to document extended follow-up. Future research to better understand which subgroups of CVID patients have post-operative complications is important to help determine transplantation candidacy.

## Conclusions

We report a case of successful heart transplantation for GCM in a patient with CVID and no major infectious complications after 2 years of follow-up. To our knowledge, this is the second reported case of

GCM in a patient with CVID and the first in an adult. Common variable immunodeficiency should not be considered an absolute contraindication to heart transplantation.

## Lead author biography



Thomas Franzon is a current general cardiology fellow at the University of Michigan in Ann Arbor, Michigan. He completed his internal medicine residency at the University of Pennsylvania and his medical degree at the State University of New York, Upstate Medical University. He will begin a two-year electrophysiology fellowship after completing his general cardiology fellowship.

## Supplementary material

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

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

**Consent:** The authors confirm that written consent for the submission and publication of this case, including images, has been obtained from the patient in line with COPE guidance.

**Conflict of interest:** None declared.

**Funding:** None declared.

## References

- Resnick ES, Moshier EL, Godbold JH, Cunningham-Rundles C. Morbidity and mortality in common variable immune deficiency over 4 decades. *Blood* 2012; **119**:1650–1657.
- Chapel H, Lucas M, Lee M, Bjorkander J, Webster D, Grimbacher B et al. Common variable immunodeficiency disorders: division into distinct clinical phenotypes. *Blood* 2008; **112**:277–286.
- Hill AT, Thompson RA, Wallwork J, Stableforth DE. Heart-lung transplantation in a patient with end-stage lung disease due to common variable immunodeficiency. *Thorax* 1998; **53**:622–623.
- Montalti R, Mocchegiani F, Vincenzi P, Svegliati Baroni G, Nicolini D, Vivarelli M. Liver transplantation in patients with common variable immunodeficiency: a report of two cases. *Ann Transplant* 2014; **19**:541–544.
- Laufs H, Nigrovic PA, Schneider LC, Oettgen H, Del NP, Moskowitz IPG et al. Giant cell myocarditis in a 12-year-old girl with common variable immunodeficiency. *Mayo Clin Proc* 2002; **77**:92–96.
- Chen Y, Cameron A. Aspergillosis after liver transplantation in the context of common variable immunodeficiency: case report. *Transpl Infect Dis* 2013; **15**: 540–544.
- Murakawa Y, Miyagawa-Hayashino A, Ogura Y, Egawa H, Okamoto S, Soejima Y et al. Liver transplantation for severe hepatitis in patients with common variable immunodeficiency. *Pediatr Transplant* 2012; **16**:E210–E216.
- Gow PJ, Mutimer D. Successful outcome of liver transplantation in a patient with hepatitis c and common variable immune deficiency. *Transplant Int* 2002; **15**: 380–383.
- Bjoro K, Skaug K, Haaland T, Frøland SS. Long-term outcome of chronic hepatitis c virus infection in primary hypogammaglobulinaemia. *QJM* 1999; **92**: 433–441.

10. Smith MS, Webster AD, Dhillon AP, Dusheiko G, Boulton R, Savage K et al. Orthotopic liver transplantation for chronic hepatitis in two patients with common variable immunodeficiency. *Gastroenterology* 1995;**108**:879–884.
11. Azzu V, Elias JE, Duckworth A, Davies S, Brais R, Kumararatne DS et al. Liver transplantation in adults with liver disease due to common variable immunodeficiency leads to early recurrent disease and poor outcome. *Liver Transpl* 2018;**24**: 171–181.
12. Aguilera I, Sousa JM, Gómez-Bravo MA, Núñez-Roldán A. De novo autoimmune hepatitis after interferon treatment in a liver transplant recipient with common variable immunodeficiency. *Dig Liver Dis* 2014 Jul 1;**46**:663–664.
13. Mahdavinia M, Mirsaeidi M, Bishehsari F, McGrath K. Primary sclerosing cholangitis in common variable immune deficiency. *Allergol Int* 2015;**64**: 187–189.
14. Jørgensen SF, Macpherson ME, Bjørø K, Karlsen TH, Reims HM, Grzyb K et al. Liver transplantation in patients with primary antibody deficiency. *J Allergy Clin Immunol* 2017;**139**:1708–1710.
15. Farmer JR, Sokol CL, Bonilla FA, Murali MR, Kradin RL, Astor TL et al. Bilateral lung transplantation in a patient with humoral immune deficiency: a case report with review of the literature. *Case Rep Immunol* 2014;**2014**:1–7.
16. Burton CM, Milman N, Andersen CB, Marquart H, Iversen M. Common variable immune deficiency and lung transplantation. *Scand J Infect Dis* 2007 Jan;**39**: 362–367.
17. Shah H, Kumar P. Successful lung transplantation in a CVID patient with recalcitrant bronchiectasis. *J Allergy Clin Immunol* 2013;**131**:AB153.
18. Thickett KM, Kumararatne DS, Banerjee AK, Dudley R, Stableforth DE. Common variable immune deficiency: respiratory manifestations, pulmonary function and high-resolution CT scan findings. *QJM* 2002;**95**:655–662.
19. Lund KP, Bruunsgaard H, Marquart HV, Sørensen SS. Case report: renal transplantation in patients with pre-existing hypogammaglobulinemia. *Scand J Immunol* 2017;**86**:113–117.
20. Al Nimri O, Rajput A, Martinez E, Fahrenholz JM, Paueksakon P, Langone A et al. Acute rejection of a kidney transplant in a patient with common variable immunodeficiency: a case report. *Transplant Proc* 2017;**49**:380–385.
21. Kandolin R, Lehtonen J, Salmenkivi K, Räisänen-Sokolowski A, Lommi J, Kupari M. Diagnosis, treatment, and outcome of giant-cell myocarditis in the era of combined immunosuppression. *Circ Heart Fail* 2013;**6**:15–22.
22. Cooper LT. Giant cell myocarditis: diagnosis and treatment. *Herz* 2000;**25**: 291–298.