Peer Review File

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Reviewer A

This is an excellent paper that is highly suggestive in clinical cases. Some corrections would be requested.

Authors' response: We would like to thank the reviewer for the careful evaluation of our manuscript and the comments above.

①Figure1
Line 411, 412 Figure 1: *A*→A 1*B*→1B
Please correct italics.

Reply 1: As requested A and B in Figure 1 and Figure 2 legends were changed to italic.

Add calibration to the ECG.

Authors reply: Thank you. "25 mm/sec" was added to Figure 1B.

Line 414
(PVC) should be deleted because it does not appear in the text that follows.

Authors reply: "PVC" was removed both from the main text and Figure legends.

②
Line 119
(red arrow) in the text should be deleted.

Authors reply 2: As requested, (red arrow) was deleted in the main text.

③ Figure2
Line 416, 418 Figure 1: *A*→A 1*B*→1B
Please correct italics.

Authors reply 3: As mentioned in our Reply 1, *A* and *B* in Figure 2 legends were changed to italic.

Line 418
RA, right atrium; should be deleted because it does not appear.
On the other hand, please include IVS, interventricular septum; PWT, posterior wall; LA, left atrium.

RV, right ventricle; LV, Left ventricle.→LV, left ventricle
Please change to lower case

Authors reply: Apologies for these inaccuracies. We have made all changes You pointed out, and the correct text in the figure legends appears now as:

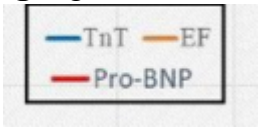
"IVS, interventricular septum; LA, left atrium; LV, left ventricle; PW, posterior wall; RV, right ventricle".

④
Line 123
(N-terminal pro-BNP) →(NT pro-BNP) **Please fix it.**
Isn't pmol/L a mistake for ng/L? In Line180, you use ng/L.
Line 124
C-reactive protein (CRP) at 35 ml/L.
Isn't ml/L a mistake for mg/dL?

Authors reply 4: We measured pro-BNP at the time patient was admitted, not NT pro-BNP. We have now removed"NT or N-terminal" from the figure legends and main text. In addition, in Figure 3, Pro-BNP was changed to "pro-BNP" and Pmol/L was changed to "pmol/L". The measurement unit for pro-BNP "pmol/L" is correct. Because we have measured pro-BNP.
However, at 6 month follow, our laboratory changed its routines and started measuring NT pro-BNP instead of pro-BNP. Therefore on page 7 in outcome and follow-up section,

NT pro-BNP of 891 ng/L appears correct.
You are absolutely right, the correct unit for CRP was mg/dL and we have changed this in the main text. Thank you.

⑤Figure3



ProBNP→NT pro-BNP **Please fix it.**

Authors reply 5: As mentioned above. Pro-BNP is correct. P was changed to p.

Line 426
Pro-BNP, pro-B-type natriuretic peptide;
→NT pro-BNP, N terminal pro-B-type natriuretic peptide;

Please correct it.

Authors reply: Please see our response above. pro-BNP, pro-B-type natriuretic peptide is correct.

Isn't pmol/L a mistake for ng/L? If correct, Pmol should be changed to pmol.

Authors reply: pmol/L is correct. We have changed Pmol/L to pmol/L.

⑥ Line137, 145
The patient received 1 gram→1000 mg
methylprednisolone (1 gram O.D.)→(1000 mg)

Authors reply 6: Corrected in both sentences. OD was changed to once daily.

⑦Line147
cyclosporine (aimed at 100-150 *ng*/ml)→cyclosporine (aimed at 100-150 ng/ml)
Please correct italics.

Authors reply 7: Corrected italics.

⑧mycophenolate mofetil (1 gram BID)→(1000 mg)
BID should be deleted. List only the total daily dose.

Authors reply 8: 1 gram was changed to 1000 mg and BID changed to twice a day. If we shall write 1000 mg, the readers will be wondering whether this was given once or twice a day, or if we write 2000 mg, the question will arise whether it was given once or by divided doses. Therefore, in our view it is important to be more precise regarding the dosage and frequencies of immunosuppressive treatment.

⑨Line167
What is OMM?

Authors reply 9: We have replaced OMM with optimal medical management. The correct sentence reads now as:

"The patient was stabilized on immunosuppressive treatment and optimal medical management for heart failure, and remained in hospital for 46 days."

⑩Line172
mofetil (1 g BID) →(1000 mg)

Authors reply 10: Changed to 1000 mg twice a day.

⑪Line173
treated with ramipril 5 mg BID→ **BID should be deleted. List only the total daily dose.**
metoprolol 200 mg OD.→O**D should be deleted**
He was also put on apixaban 5 mg BID → **BID should be deleted. List only the total daily dose.**

Authors reply 11: Thank you. As request all changed on cardiac medications were made. Please see page 7.

⑫**Line** 177
At 6-month follow-up, LVEF increased to 60% (*Video 2*) and remained stable (55%)
178 at 4-year follow-up (*Video 3A-3B*)→**Please correct italics.**

Authors reply 12: Corrected, italics.

⑬**Line 180, 181**
N-terminal pro-BNP 890 ng/L →**NT-pro-BNP**
CRP 1 mg/L →1 **mg/dL**

Authors reply 13: Thank you. Changed to NT pro-BNP and mg/dL. Sorry for the inaccuracy.

⑭**Line253**
"ECMELLA"→ECPELLA？？？

Authors reply 14: Both ECMELLA and ECPELLA have been used in the literature.

However, we agree it is probably more common to use ECPELLA, and we have changed this now to "*ECPELLA"*.

⑮Line437
Figure 6: Cardiac magnetic resonance (CMR)
(CMR) should be deleted because it does not appear in the text that follows.

Authors reply 15: CMR was deleted.

⑯Line450
Video 3A/3B: Echocardiography, apical 4-chamber (3*A*) and apical 2-chamber (3*B*)
Please correct italics.

Authors reply 16: Done.

⑰Did this case have ocular symptoms? It has been reported that the preceding ocular symptoms may be a precursor to giant cell myocarditis (doi: 10.1016/j.cjca.2023.03.016.). Please add this to your text as it is one of the findings that may be suspicious for giant cell myocarditis and is important.

Authors reply 17: Thank you for this important comment and reference. We have added the following new text to the Discussion, page 14 (line 303-308):

"In addition, some patients with GCM may present with ocular symptoms (18). In the literature, a total of 10 cases of GCM with orbital myositis or other ocular symptoms have been reported (22-24). Orbital myositis is a nonspecific inflammatory disorder of the extraocular muscles, and is generally considered an autoimmune disease."

Further, the following sentence in the same paragraph was modified as:

"Of note, our patient had a previous history of autoimmune disease (Lichen planus) but did not report any ocular symptoms."

Reviewer B
Based on the provided citations, it appears that the article discusses a case study of a patient with giant cell myocarditis (GCM) and provides valuable information on the diagnosis and treatment of this rare condition. The authors emphasize the importance of early diagnosis, endomyocardial biopsy, access to mechanical circulatory support, and immunosuppressive treatment in managing GCM. They highlight the use of methylprednisolone to reduce myocardial inflammation, sustained immunosuppressive treatment, and optimal heart failure medications for myocardial recovery and long-term stabilization. The article also discusses the choice of mechanical circulatory support, such as VA-ECMO or Impella, and includes references, figures, and videos to support the information provided.

Overall, based on the limited information available, the article seems to be informative and comprehensive in addressing the case study and providing insights into the management of GCM. Overall, the language used in the paper appears to be of high quality, providing detailed information on the patient's treatment and outcomes, as well as referencing relevant diagnostic and imaging

techniques.
Based on the provided citations, there are a few areas where the article could be improved:

1. Lack of prospective studies: The article mentions that our understanding of predictors of response to immunosuppressive therapy and the optimal duration of treatment is limited [2]. It would be beneficial to include a discussion on the need for future prospective studies to address these knowledge gaps [2].

Authors' response 1: We thank the reviewer for the thorough evaluation of our paper and helpful comments. Regarding the need for future prospective studies, we have added the following sentence to the last part of Discussion, page 14 (line 317-323):

"Overall, there is little evidence in the literature from prospective studies. To address the existent knowledge gaps in the field, there is need for well-designed prospective research studies. Furthermore, when dealing with the effectiveness of treatments, RCTs provide the most reliable source of evidence for treatment recommendations, reducing the chance of bias. To our knowledge, no proper RCTs have been performed to evaluate the effectiveness of immunosuppressive therapy in GCM, and this should be the aim of future research."

2. Lack of randomized controlled trials (RCTs): The article mentions that no RCTs have been performed to evaluate the effectiveness of immunosuppressive therapy in GCM [4]. It would be helpful to highlight the importance of conducting RCTs to establish evidence-based treatment protocols for GCM.

Authors reply 2: Thank you for this important comment highlighting the need for RCTs. As mentioned above, we have added the following text to page 14 (just above main Conclusions):

"Overall, there is little evidence in the literature from prospective studies. To address the existent knowledge gaps in the field, there is need for well-designed prospective research studies. Furthermore, when dealing with the effectiveness of treatments, RCTs provide the most reliable source of evidence for treatment recommendations, reducing the chance of bias. To our knowledge, no proper RCTs have been performed to evaluate the effectiveness of immunosuppressive therapy in GCM, and this should be the aim of future research."

3. Limited discussion on right ventricular function: The article briefly mentions the challenges in evaluating right ventricular function in patients on VA-ECMO [4]. Expanding on this topic and discussing potential strategies for assessing and managing right ventricular dysfunction would enhance the article's comprehensiveness.

Authors reply 3: Thank you for bringing this important issue to our attention. As requested, we have expanded on this topic, and thoroughly discussed the importance of right ventricular function assessment and the methodology of choice for this. The following new paragraph was added to page 11 in the Discussion (line 231-252):

"The evaluation of right ventricular function of patients on VA-ECMO can be challenging. Generally, because of the complex anatomy of the right ventricle, precise function assessment is difficult. Moreover, recent case reports have shown that in fulminant heart failure due to GCM, the pattern of reverse remodelling may be different between left ventricle and right ventricle (12). Prednisolone and ciclosporin treatment resulted in the right ventricular function recovery and improvement of heart failure symptoms, while the LV function (LVEF) did not recover. Of note, right ventricular function, a low pressure system, was assessed by fractional area change, an echocardiographic measure which has been shown to correlate better with cardiac magnetic resonance imaging-derived right ventricular ejection fraction than with TAPSE (13). TAPSE is a standard measure of right ventricular systolic function, but is load dependent and may be normal until late stage and in case of tricuspid regurgitation (14). By contrast, right ventricular systolic velocity (S') and right ventricular fractional area change are considered as the measurements of choice in defining right ventricular function in critically ill patients, and right ventricular free wall strain is a better predictor of mortality than TAPSE or right ventricular S'. Furthermore, the novel right ventricular-pulmonary artery coupling markers derived from either TAPSE/systolic pulmonary artery pressure ratio or fractional area change/SPAP ratio seems to provide additional information about the causes and consequences of right ventricular impairment in patients with significant tricuspid regurgitation or critically ill Covid-19 patients (14-15). However, there are very limited data available on the assessment of right ventricular function in GCM patients, particularly right ventricular-pulmonary artery coupling markers. The clinical significance and prognostic impact of these important non-invasive markers of right ventricular function warrant further investigation in GCM patients. RV evaluation while on ECMO needs multifaceted approach with echo and invasive parameters. While turning down the ECMO rpm, less unloading and higher preload of the RV occurs. In case of recovery, RV ECMO functional parameters improve, central venous pressure maintains within acceptable range, SVO2 is maintained or improved and LV responds positively to increased preload with output increase and wedge pressure within acceptable values. In the opposite case, RV and LV recovery is limited and weaning may be difficult."

4. Inclusion of more recent data: The article cites studies from 2009 to 2021 [4]. It would be beneficial to include more recent studies to provide an up-to-date overview of the management of GCM.

Authors reply 4: In our paper, we had quoted important historical studies back from 1985, 1990 and 1997 – and the more recent data from 2009 to 2021 as you mentioned.

However, following comments from Yourself and reviewer#1, we now have added 5 more new references involving case series or research studies on GCM. There are lots of publications on GCM in the literature. However, we have chosen to cite only those original studies and case series which have direct relevance for our work and omitted studies and case reports with confirmatory findings.

5. Can you please provide more details on the indication for the dual-chamber ICD implantation in this case?

Authors reply 5: As illustrated in Figure 3, at discharge (day 46) his ejection fraction was just below 40%. Given the fact that at presentation he was critically ill and experienced ventricular tachycardia leading to circulatory collapse, we deemed a secondary prophylactic ICD necessary for this patient. In recent years there has been increased awareness of recurring ventricular arrhythmias after the patient has recovered from myocarditis the European guidelines now recommend the consideration of ICD prior to discharge in patients who have experienced VT or VF with circulatory compromise during the acute phase of myocarditis (Class IIa, leve of evidence C).

Katja Zeppenfeld et al, 2022 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: Developed by the task force for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death of the European Society of Cardiology (ESC) Endorsed by the Association for European Paediatric and Congenital Cardiology (AEPC), European Heart Journal, Volume 43, Issue 40, 21 October 2022, Pages 3997–4126, https://doi.org/10.1093/eurheartj/ehac262

We have modified the following paragraph in Case Description, page 7:

"On last echo before discharge, LVEF was just below 40%. Given the fact that at presentation he was critically ill and experienced ventricular tachycardia leading to circulatory collapse, we deemed a secondary prophylactic ICD necessary for this patient. Therefore, a dual-chamber ICD was implanted prior to discharge."