

Peer Review File

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Reviewer A

Immune myocarditis is typically described as immune checkpoint inhibitor myocarditis (ICI myocarditis). You could consider incorporating this abbreviation into your write-up to ensure consistency with other work on the topic. Immune myocarditis could be confabulated with autoimmune myocarditis, or immune mediated myocarditis, which is not necessarily the same as ICI myocarditis.

Consider a non-single letter abbreviation for thymoma

Use active voice – “conventional chemotherapy is used” rather than “has been used”

Please place citations at the end of the line. Do not state “previous research has shown” – this is inferred by use of citation.

Reply: We agree with the reviewers' suggestions and will incorporate the recommended changes into the manuscript. We have made a change in line 2, 11, 73, 83, 307, 310, 352, 354.

Abstract

Line 27 – “explosive myocarditis” should be relabeled as fulminant or recategorized based on an established grading system.

Line 29/31 – This study aims to examine treatment of thymic epithelial tumor-associated immune myocarditis

Line 44 – what is meant by corticosteroid shock therapy? Do you mean pulse steroids? Or ICD therapy.

Reply: We agree with the reviewers' suggestions and will incorporate the recommended changes into the manuscript. We deleted “shock” in line 44.

We have made a change in line 27,29,30,44.

Introduction

Paragraph – consider splitting this into more than 2 sentences

Line 71 – Please include citations at the end of the sentence. It is acceptable to just make a statement, then add your citation, rather than citing as done in line 71. This line is phrased in the passive and uses “has shown” twice in an unnecessary way.

83 – please clarify what is meant by TMB. Please list citations at the end of the sentence.

86 “– ...TET tumors.” Should be rewritten as “TET” as the acronym already has the word Tumor in it.

98 to 100 – ICI myocarditis is arguably not rare, depending on the definition used. It might be more appropriate to reflect on the fact that it is a novel discovery with low case ascertainment. Further, the effects are not at all subtle – these patients often present with syncope, severe

myositis or myasthenic syndrome with a troponin in the thousands.

Reply: We agree with the reviewers' suggestions and will incorporate the recommended changes into the manuscript.

We have made a change in line 71,83,84,98-101.

Case presentation

The case descriptions have several errors or key pieces of missing information. Further, in one of the cases, infliximab is used for ICI myocarditis. This is a controversial move as a case control study has demonstrated a 12 fold increase in odds of death with use of infliximab :

Cautela J, Zeriouh S, Gaubert M, Bonello L, Laine M, Peyrol M, Paganelli F, Lalevee N, Barlesi F, Thuny F. Intensified immunosuppressive therapy in patients with immune checkpoint inhibitor-induced myocarditis. *J Immunother Cancer*. 2020 Dec;8(2):e001887. doi: 10.1136/jitc-2020-001887. PMID: 33298621; PMCID: PMC7725077.

<https://pubmed.ncbi.nlm.nih.gov/33298621/>

Abatacept, despite limited data, has become more frequently accepted as intensified immunotherapy of choice, although plasma exchange and IVIG are also widely used.

There is very little data on arrhythmogenic events, and equally little data on other comorbid conditions. ICD-P insertion is also an intervention which should be considered in cases of ICI myocarditis associated with cardiac arrest as it is associated with improved survival time.

<https://link.springer.com/article/10.1186/s40959-023-00185-y>

Finally, in one of these cases, immunotherapy is given to a patient with pre-existing myasthenia gravis. This is a very controversial move, as many institutions would view this as an absolute contraindication to receiving immunotherapy.

120 - of the tumor cells

123 – Please present PR and QRS intervals as these have prognostic significance. This ECG demonstrates a bundle branch morphology. Please provide a more detailed description of the conduction delays present in this ECG.

125 – please clarify what diagnostic criteria were used, and what level of certainty and grade of myocarditis was present.

127 – please clarify if respiratory failure was hypercapnic, hypoxic or both. Why did the patient develop respiratory failure?

131 – what type of cardiac arrest? Was it bradycardia arrest, PEA arrest?

132 – why were beta blockers used? What other antiarrhythmics were used and what was their rational for use?

135 – it sounds like this patient may have presented with decompensated heart failure – did they develop cardiogenic shock?

136 – This ECG shows ventricular tachycardia, not ventricular flutter. Ventricular flutter is not

a term used to describe ventricular arrhythmias.

Was an ECG performed?

What sort of arrhythmias developed?

Please mention the name of the steroid used, in addition to the dose.

Please include echocardiogram results.

Reply: We agree with the reviewers' suggestions and will incorporate the recommended changes into the manuscript.

We have made a change in line 122,135-136.

140 – “Had failed multiple lines of chemotherapy, including...”

143 – what is meant by acute thoracic depression? Chest pain?

150 – was this the results of the Echocardiogram? ECG doesn't diagnose heart failure.

149 - I cannot see T-wave abnormalities on Figure 2 A, please identify which lead you have noted T wave abnormalities.

151 – please describe if this patient met any of the available diagnostic criteria for ICI myocarditis.

161/163 – The associated images are very helpful in illustrating treatment response. Please list the treatments used in the text.

Reply: We agree with the reviewers' suggestions and will incorporate the recommended changes into the manuscript.

We have made a change in line 142,145,152,166-170.

Information and search strategy

The search strategy is unclear – it appears the authors searched for the key words, and then listed a PICO strategy. There is no mention of what types of studies were included. When presenting the search terms used, the Boolean operators used are a bit unclear (there is no use of brackets to clarify if ANDs refer to groups of operators or to a single operator).. It is not entirely clear if the author understands that the PICOT mnemonic is supposed to help them develop a search strategy which incorporates Boolean operators.

My biggest criticism of the methodology is reliance on a single database. For a systematic review, the standard should be 3-5 databases. For a piece of original research 1-2 databases may be acceptable, however this paper markets itself as a literature review.

Paragraphs 205/216 – could be condensed to a line and the tables included.

Was a systematic review guideline document adhered to? Eg PRISMA? It would be worth listing if this was the case. There is a clearly listed process for case selection and exclusion, so I would imagine the study is largely adherent to PRISMA guidelines.

Consider discussing the cases separately based on study type – this is more useful in that cases described in case reports will suffer from selection bias whereas clinical trial/cohorts will not have the same issue.

Reply: We agree with the reviewers' suggestions and will incorporate the recommended changes into the manuscript.

We have made a change in line 212-216.

Discussion

The major concern with using ICI therapy in thymic neoplasia is the concern that these patients may be more prone to ICI toxicity compared to patients without thymic neoplasia. The discussion addresses this in part, however it is not clear if the data discussed in lines 294/315 is specific thymic neoplasia. If any of the included papers do address this, it would be worth mentioning this. If they don't then that is also a very interesting finding.

335 – This is the mortality risk, not the mortality rate. Rate requires the use of event-per-unit-time.

329/351 – this section gives a very interesting description of the available data and provides helpful insight into the pathophysiology of the disease. Please do not include the lead author in the text, and place the citation at the end of the study. Please clarify if the cohort data is specific to thymic neoplasia.

353/364 – the study by Cautela should definitely be mentioned at this point.

Reply: We agree with the reviewers' suggestions and will incorporate the recommended changes into the manuscript.

We have made a change in line 294,315,336,337,341.

Paragraph 366 – this is a case series, not a cohort study, so the comment about small sample size might be better reframed as “we present two cases of severe ICI myocarditis”, followed with a line about the issues with case ascertainment of ICI myocarditis. The value of the case series is to describe the course of the disease.

Discussion stratified by study type might be a helpful approach to presenting data. Data from case reports will be in narrative format, and is well described in the text. It is unclear how much data from cohort studies and clinical trials is applicable to patients with thymic neoplasia.

Reply: We agree with the reviewers' suggestions and will incorporate the recommended changes into the manuscript.

We have made a change in line 371.

Reviewer B

- 1) First, the abstract is not adequate and needs substantial revisions. The background needs to explain the uniqueness of the two cases and why both are deserved to be reported. The case presentation part needs to focus on the two cases that the authors want to report, focusing on their disease history, treatment, clinical presentations of myocarditis, its treatment, and prognosis. The authors only need to briefly mention what has been found in the literature and compare with the two cases. The conclusion should not focus on the efficacy of immunotherapy. Please have comments on the early recognition of myocarditis and its management, as well as lessons learned from this case. The abstract and the whole paper should be strictly rewritten according to the CARE guideline.

Reply: We agree with the reviewers' suggestions and will incorporate the recommended changes into the manuscript.

We have made a change in discussion.

- 2) Second, the introduction needs to focus on immune myocarditis in thymic epithelial tumors patients receiving ICIs. It is not necessary to review the efficacy and mechanisms of ICIs. Please review what has been known on irAE, the frequency of immune myocarditis, its treatment and prognosis. Importantly, please clearly analyze the novelty and the clinical significance of the two cases.

Reply: We agree with the reviewers' suggestions and will incorporate the recommended changes into the manuscript.

We have made a change in introduction and discussion.

- 3) Third, in the case presentation, please provide the timeline of the two cases to depict the cancer treatment, progression, detection of myocarditis, its treatment and prognosis.

Reply: We agree with the reviewers' suggestions and will incorporate the recommended changes into the manuscript.

We have made a change in Case presentation.

- 4) Fourth, the literature review part should focus on the immune myocarditis in thymic epithelial tumors, not to review studies of thymic epithelial tumors undergoing ICIs. The efficacy of ICIs is also not the focus of this review.

Reply: We agree with the reviewers' suggestions and will incorporate the recommended changes into the manuscript.

We have made a change in literature review.

- 5) Finally, please cite several related papers: 1. Rajan A, Mullenix C, Shelat M, Zhao C. The role of immunotherapy for management of advanced thymic epithelial tumors: a narrative review. *Mediastinum* 2021;5:23. 2. Xiang J, Si J, Hao Y, Wei J, Wang W, Guan Y, Xu C, Song Z. Efficacy and safety of immune checkpoint inhibitors (ICIs) combined with antiangiogenic therapy for thymic epithelial tumors (TETs): a retrospective study. *Transl Cancer Res* 2023;12(3):550-557. doi: 10.21037/tcr-22-2192. 3. Song X, Fan J, Zhu L, Wang Z, He Y, Zhou C. The efficacy and safety of immunotherapy in thymic epithelial tumors: more effective, more risky: a systematic review. *J Thorac Dis* 2021;13(8):5093-5103. doi: 10.21037/jtd-21-290. 4. He Y, Chen W, Cai J, Luo C, Zhou C, Wei L. PD-1 inhibitors-associated myocarditis in non-small cell lung cancer patients. *J Thorac Dis* 2023;15(9):4606-4619. doi: 10.21037/jtd-23-596.

Reply: We agree with the reviewers' suggestions and will incorporate the recommended changes into the manuscript.

We have made a change in introduction.