Author’s response to reviews

Title: Myocardial Oedema in an 8-year-old Chinese Boy with Idiopathic Systemic Capillary Leak Syndrome

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Author’s response to reviews:

We thank the reviewers for their constructive comments, which we the authors believe have improved this manuscript. All comments/suggestions by the reviewers have been addressed and changes in the text are highlighted in yellow.

REVIEWER COMMENTS TO AUTHORS:

Reviewer: 1 (Dr Gregorio Milani)

1) The title is too long. I suggest author to reword it as follows: Myocardial Oedema in an 8-year-old Chinese Boy with Idiopathic Systemic Capillary Leak Syndrome

We have modified the title to “Myocardial Oedema in an 8-year-old Chinese Boy with Idiopathic Systemic Capillary Leak Syndrome” (lines 1 to 2) as suggested.

2) English should be revised by a native English speaker with experience in scientific publication (e.g. "A Chinese boy with a medical history of eczema and obesity presented
with two separate episodes of hypovolemic shock at six and eight years of age." (the term "separates" is not appropriate and is superfluous)

The manuscript has been revised by a native English speaker with experience in scientific writing.

3) The authors do not report crucial clinical data of the patient (cardiac frequency, blood pressure values, signs of shock, weigh gain...)

We have included the crucial clinical data of the patient as suggested by the reviewer (lines 109 to 111, 122 to 124, 141 to 148, 166 to 169). However, the child was critically ill and too unstable for precise weight measurements during his hospitalization in the intensive care unit.

Authors do not report important findings to confirm the diagnosis of ICLS: e.g. absence of urinary proteins

We have now included the results of the urine immunofixation and the absence of urinary proteins. More details regarding our workup for infection and septic shock have also been added. (lines 155-158)

4) The current discussion appears as both a narrative review and a sort systematic review. I suggest the authors to simplify the discussion, avoiding any information on the search strategy (that otherwise would appear poorly documented) and limiting it to cardiac findings associated to ICLS and, maybe, to therapeutic approach available in the literature

Our discussion has been simplified to focus on the cardiac findings associated with ICLS and the therapeutic approach as suggested by the reviewer. The discussion on ‘search strategy’, ‘clinical features of systemic capillary leak syndrome’, ‘diagnosis of systemic capillary leak syndrome’ and ‘prognosis and outcome’ was removed.

5) I wonder why authors do not include ref 19 among pediatric cases?

6) Discussion must be shortened at least of 30%. There is currently a disproportion among discussion and the other sections of the manuscript

The discussion has been revised and shortened by approximately 30% (from 2042 to 1367 words) according to the reviewer’s suggestion.

7) Table 1 do not contain all pediatric case reports. I suggest author to remove it since they do not perform a systematic review. If authors decided to perform a systematic review, they should follow PRISMA guidelines

Table 1 has been removed as suggested by the reviewer.

8) Figure one is very difficult to read. Please upload a good quality figure

A higher resolution of Figure 1 has been uploaded.

9) Are the authors sure that all the information contained in figure 2 are essential?

Figure 2 is now revised to a short-axis view where the thickened myocardium can be better appreciated. The information in Figure 2 was revised and only the most essential echocardiographic description is included in the text. In addition, post-event normalization images were added for comparison as recommended by reviewer 2.

10) In conclusion the manuscript is potentially interest, however the manuscript should be more carefully reported, extensively edited and simplified

We thank the reviewer for the above suggestions which significantly improved this manuscript after it has been revised accordingly.
Reviewer: 2 (Dr Steve Leung)

The authors present an interesting case of systemic capillary leak syndrome. The authors states that this is the first pediatric case to demonstrate myocardial edema requiring ECMO support. The case presentation describes the typical presentation of an SCLS patient. However I have the following concerns/recommendations:

1) This case presentation of the myocardial edema would be strengthened if the authors can provide 2D echo images (with measurements) of the thickened myocardium, and post-event normalization for both presentations. Providing the myocardial mass may be appropriate, as the chamber size can change, which can change the wall thickness of the myocardium (i.e. smaller chamber size, can have thicker walls with the same myocardial mass. Thus the thickness is not related to edema, but due to a change in myocardial mass distribution).

Echocardiogram for the patient’s first presentation was performed at another hospital, and therefore it is not available to us. The short-axis view with measurements of the thickened myocardium at presentation to us and post-event is now added for comparison. The ventricular mass index is also provided. Since the thickened myocardium can be better appreciated on the 2D images, the M-mode images were removed.

2) Was there blood culture results for the 2nd presentation?

Blood culture was negative and this information has now been added to the manuscript. (line 155)

3) Figure 2 (echo image) measurements appear to be incorrect as the IVS measurement crosses into the RV. Systolic function should be given as an ejection fraction based on at least a biplane measurement, rather just state "poor systolic function".

The systolic function was re-measured based on a more appropriate recognition of the IVS and LVPW border. (line 146)

4) Would recommend providing a normal range of lab values for IgG from which this assay was used to measure.

We have added the IgG reference range of 724-1380 mg/dL to the manuscript. (line 157)
5) Regarding some of the hospitalization description, it would be good to state hospital day when certain events occurred. This may be described in the figure, but I was unable to read the text or numbers on the figure (blurred). Please include laboratory units.

A higher resolution of Figure 1 has been uploaded. Additionally, the timing of significant events has been added to the text. (line 124, line 133, line 135-136, line 152, line 162)

6) DISCUSSION: 3rd paragraph 3rd sentence, would change "first known case of ISCLS" to "first reported case of ISCLS".

The sentence has now been changed to ‘Our patient is the first reported case of ISCLS in the Chinese population’ according to the reviewer’s suggestion. (line 189-190)

7) Cardiac Involvement section: 3rd sentence: please provide your diastolic function data to support the reported "impaired ventricular filling" (e.g. E, A, e' etc).

We have rephrased our sentence to ‘ventricle was underfilled due to distribution of intravascular volume by capillary leak’ instead of ‘impaired ventricular filling’. (line 196-197)

8) Last paragraph of Acute Treatment: Compartment syndrome can occur in the arms. May generalize "peroneal nerve damage" to just "nerve damage".

The sentence has now been changed to ‘Cautious fluid replacement, diuretics, early involvement of the orthopaedic surgical team and strict surveillance of the peripheral limb intracompartmental pressure may reduce muscle and nerve damage’. (line 257-258)

9) Second to last paragraph in Prophylactic treatment: Would correct the duration of symptom free... this states ten months, whereas the last sentence in the case presentation states 12 months.

It has now been changed to 12 months. (line 291)