Peer Review File

Article information: https://dx.doi.org/10.21037/jeccm-22-22

First External Peer Review

Reviewer A

Comment 1:
The case does not provide novel insights into the syndrome. The diagnosis is not definitive but after excluding other conditions. There is no evidence that the effectiveness of the IVIG.
Reply 1:
Indeed, the case report does not show novel insights into the syndrome. However it does show the importance of the recognition of the syndrome, because of the dramatic long-term disabilities in the described patient. To prevent this we categorized symptoms into major and minor criteria to ease the diagnosis. By diagnosing the syndrome earlier complications may be prevented by giving the right treatment, eg more aggressive fluid resusicitation instead of vasopression. And although the treatment with IVIG isn't validated in RCT's, there are multiple succesfull case reports reported, which is why we suggested this treatment option.

Reviewer B

Summary:
The authors highlight the case of a middle-aged female with a history of core rod myopathy presenting with two flares of SCLS, the first diagnosed as an ISCLS, and the second constituting a COVID-19-induced SCLS. The latter was treated with IVIG although subsequent acute kidney injury required renal replacement therapy and the patient showed permanent kidney damage with a clearance of 30mL/min.
Major issues:
Comment 1:
This article brings no new knowledge in regard to the current available literature on SCLS as the first episode was probably an ISCLS acute phase, and the second one a COVID-19-triggered SCLS flare. ISCLS is now quite well described in literature although still featuring unclear pathophysiological patterns, and thus lacking of strong treatment recommendation. As for the second entity, SCLS has been recently largely reported in both COVID-19 infected patients [Knox et al. 2021; Cheung et al. 2021; Buj et al. 2022; Wu et al. 2021] and vaccinated population against SARS-CoV-2 [Matheny et al. 2021; Robichaud et al. 2021; Buj et al. 2021; Choi et al. 2021; Buj et al. 2022].

Regarding treatment, the authors do not propose new insights as IVIG is the only treatment to have showed successful prevention of relapses. As for its use during flares, it is still controversial and case-report based.
Reply 1:
COVID-19 triggered SCLS has been described in case reports before. However the combination of (unrecognized) ISCLS and then triggered SCLS we found illustrative.
Regarding treatment, we indeed did not suggest new insights. However by summarisizing current literature and potential pathophysiological targets for treatment we hopefully encourage other investigators in doing further research.

Minor issues:
Comment 1:
1. Lines 55-56 – rewriting is necessary as the formulation is strange. Did the patient present an actual respiratory failure due to COVID-19 and requiring invasive mechanical ventilation? Did pulmonary edema cause the actual respiratory failure? Was she intubated prior to respiratory failure?
Reply 1: Proper comment.
Changes in text: we have modified our text as advised.

Comment 2:
2. Orthography, syntax and grammar have to be reviewed as significant errors are noted
Reply 2: We did another critical review of our text and made some modification.

Comment 3:
3. Normal range of lab values should be added in Table 1.
Reply 3:
Changes in text: we have modified our text as advised

Comment 4:
4. The authors should specify the delay between ICU admission and IVIG onset, the reoccurrence or not of IVIG administration, the delay between ICU admission and complications (compartment syndrome).
Reply 4:
Changes in text: we have modified our text as advised

Comment 5:
5. Lines 73-74 – the authors should insist on the fact that not only the dosage but also the choice of the vasopressor used likely impacted on the outcome – necrosis of the left leg – as vasopressin is already known for its risks of extremity necrosis. [Coskun et al. 2014; Jain et al. 2021; Busta Nistal et al. 2021]
Reply 5:
Changes in text: We have modified our text as advised

Comment 6:
6. If available, the weight should be added on Figure 1 and Table 2.
Reply 6:
Unfortunatelly we do not have the patients weight during the ICU admission.

Comment 7:
7. Line 96-97. This sentence does not apply for ISCLS in which no evident cause leads to the prodromal phase. Authors should rephrase.
Changes in text: We have modified our text as advised

Comment 8:
8. Lines 126-130 – this paragraph is inexact and requires further information.
First, the authors should mention that flares and chronic SCLS are not the same entities and should be treated differently.
Second, the successful use of aminophylline/theophylline/terbutaline (i.e: drugs increasing intracellular cyclic AMP) have been reported. [Kapoor et al. 2010]
Third, the authors should notify the risk of acute kidney injury during the use of IVIG for SCLS flares as its use in acute phase remains controversial. [Druey et al 2017 ; Pineton de Chambrun 2017]
Reply 8:'
It is true that in case report series b2-agonists may have a positive effect on the frequency and intensity of relapses. (Druey 2010). We added this to our report.
Changes in text: We have modified our text as advised regarding the acute kidney injury in IVIG and other successful treatment options.

Comment 9:
9. Lines 130-140: ISCLS and drug-induced CLS are two different entities as stem cell transplantation are known triggers for endothelial injury and hyperpermeability.
Besides, the authors should mention that pediatric SCLS differs from adult SCLS as the largest series of SCLS in infants discarded the participation of paraproteins, thus different pathophysiological patterns are involved in adults versus pediatric SCLS. [Bozzini et al 2018] Subsequently, the example of the successful use of bevacizumab in stem cell transplantation-induced SCLS in a child does not seem accurate here and not transposable to adults.
Furthermore, if authors are to mention potential targeted therapies for SCLS, specifically with infectious trigger, they should add updates in literature on the subject, for instance regarding the use of canagliflozin. [Angé et al. 2021]
Reply 9:
Changes in text: We added your suggestions to our report.

Comment 10:
10. The dosage of IVIG is mistaken: it is g/kg and not mg/kg. Besides, there is no consensus on the dosage of IVIG for the initial and maintenance treatment though

2g/kg/day for a few days followed by 2g/kg/month then tapered to 1g/kg/month seemed to be the most commonly administered posology. [Xie et al. 2015; Mullane et al. 2019; Druey et al. 2016; Bichon et al. Sept 2021 ; Bichon et al. Nov 2021]
Reply 10: We made a mistake in the dosage formulation, it should be g/kg.
Changes in text: We have modified the text with a range of doses in maintainance therapy.

Comment 11:
11. Limits:
a. As particular genetic background are thought to emphasize the risk of SCLS, the authors should mention that their patient already suffered from a genetic condition, thus their patient was possibly at higher risk of developing SCLS than the general population. [Zhang et al. 2005; Pierce et al. 2019; Raza et al. 2019].
b. The consideration of a "successful" use of IVIG is presumptuous as the patient was left with a permanent kidney sequelae (initial AKI requiring RRT, and subsequent chronic kidney disease with a low clearance) and because the favorable outcome could also be imputable to the natural course of the disease.
Reply 11:
a. In our report we do chose not to choose to emphasize on genetic differences.
b. Sentences 129-130 already state that in our case the clinical improvement may be due to the natural course of the disease or due to IVIG.
Besides it is unclear whether the AKI was due to the IVIG treatment or due to shock/low blood pressure. The patient was already anuric at present in the emergency room.
Changes in text: We added the information that the patient was already anuric at presentation

Reviewer C

Comment 1:
This is an instructive case report.
The authors need to add data on platelet counts an coagulation screens to demonstrate that the limb ischemia was not due to Purpura fulminans. What was the CRP in both episodes?
In the last sentence of the case description replace "revalidation" by rehabilitation.
Reply 1:
We added data on platelet count. We did not measure coagulation screens or CRP daily unfortunately.
We changed revalidation to rehabilitation.

Second External Peer Review

Reviewer A

I have a further comment following the authors revision of the manuscript, which needs to be addressed before I deem this manuscript acceptable for publication:

The authors have added the platelet count data to the manuscript. The platelet counts show a clear reduction of platelet counts over time. This is consistent with disseminated intravascular coagulation (DIC). The authors need to discuss this phenomenon and justify their assumption that this patient had compartment syndrome as opposed to purpura fulminans causing limb ischemia not due to tissue pressure but clots in supplying arteries. Both DIC and isolated compartment syndrome have previously been described in capillary leak syndrome patients and this needs to be discussed with references.

Reply 1: It is true that out patient had signs of DIC. We cannot exclude thrombotic events due to DIC as a contributing factor to the limb ischemia. We added this in our case presentation. Moreover we added a sentence and reference in the discussion of the incidence of compartment syndrome as an isolated complication of SCLS even before resuscitation.

Changes in text: We added text in the case presentation about the DIC and added text and reference in the discussion about compartment syndrome as a complication of SCLS.