OPEN PEER REVIEW

Open Peer Review (OPR)

As a new feature for progressing towards transparency, we decided to open a new window for all of our editors as well as authors titled "**Open Peer Review**". We hope by this new facility, our reviewers will be more motivated and authors will be more satisfied with the review process. We believe that publishing our peer review reports could make a transparent and clear environment for all our efforts within a journal, but not all reviewers tend to publish their comments.

What is "Open Peer Review" process?

An "Open Peer Review" process is making the details of all review process (including reviewers, associate editors, and EICs comments) as "Public" as it is agreed by EIC, Authors, and reviewers.

Advantages of "Open Peer Review" process

- More transparency, constructiveness and tactful comments of the peer review process: leads to an increase in the quality of reviews
- More motivations for all involved roles in the review process
- Authors' satisfactions from the review process: Increases honesty between authors and reviewers
- Education of both authors and new students
- Prevents reviewers from following their individual agendas and leading to the detection of reviewers' conflicts of interests

You can find out more at:
https://sites.kowsarpub.com/kowsar/knowledgebase/category/tree.html#opr.html

Anesthesiology and Pain Medicine
Article DOI: 10.5812/aapm.104151
Published in: Anesthesiology and Pain Medicine: 10(4); e104151

Peer Review Report for "Clinical Management of Il-6 Driven Cytokine Storm Related to COVID-19 in a Patient with Recent Spinal Cord Stimulator Implants: A Case Report"

Author(s): Alfonso Papa, Maria Teresa Di Dato, Pietro Buonavolonta, Elisabetta Saracco, Anna Maria Salzano, Beniamino Casale

Review Timeline:

Submit Date:	9 May 2020
Revised Date:	19 Jun 2020
Accepted Date:	18 Jul 2020

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

Elliot Krames: Reviewer | **Revision** (0) 2 Jun 2020

Dear AE,
This article is important but it forgets its purpose. There is a nice introduction of COVID 19 followed by the case report. It is my belief that the case report is too verbose and lacks clarity. the reader only needs to know that this patient had an SCS device implanted for back pain and that after a certain amount of time she developed COVID and an inflammatory response to the pocket. Please shorten the case report.
I also feel that the discussion should be shortened to a discussion of COVID and the resultant cytokine storm and its relation to patients with SCS.
Finally, it would be important to suggest to your readership that they should be aware of the possibility of inflammation, not only in the pocket but in all of the implanted hardware.
Thanks.

REFEREE: Reviewer | **Revision** (0) 9 Jun 2020

Dear AE,

I have now reviewed the paper twice. It is an interesting case report of a 63-year-old woman with FBSS who underwent implantation of an SCS and IPG, who subsequently tested positive for COVID-19. After a brief period of use of hydroxychloroquine and Azithromycin, she was started on Tocilizumab. 10 days after starting treatment, she developed redness and inflammation over the battery pocket site.
- The "risk-benefit ratio" for performing tissue biopsy was felt to be unfavorable, hence she was started on Bactrim, which resolved the inflammation.
- The hypotheses of the case report are flawed. Without a tissue sample or biopsy, there can be no determination as to what was causing the inflammatory reaction around the IPG site. The opinion of the authors is that it was directly related to the implementation of the Tocilizumab; however, there is no direct or even indirect evidence that this is the case. Though the IPG was placed in December 2019, and the inflammatory reaction was identified in March 2020, it still remains within the realm of being an inflammatory reaction that has nothing whatsoever to do with COVID-19, or with the reduction in CD8 T-cell levels, or with Tocilizumab.
- My short answer for the suitability of this case report is the following: The authors have made a nice summary of many of the issues related to cytokine storm-related to COVID-19. That part of the Discussion is reasonable. The fact that a patient with a recently implanted IPG developed redness and inflammation over the battery site a few weeks following implantation, without a tissue biopsy, does not implicate Tocilizumab. The ESR was 60, which simply indicates severe inflammation. There was no reporting of a CRP serum level. That might have been useful. The empiric use of Bactrim for 7 days might have treated any number of bacterial infections, including methicillin-resistant Staphylococcus aureus (MRSA), which might have been the cause of the inflammation. In fact, the identification that improvement was forthcoming following the use of Bactrim tends to rule in a bacterial etiology, and rule out an inflammatory type of condition related to Tocilizumab. A simple inflammatory type of condition should not have responded to an antibiotic. Antibiotics treat bacterial infections, not alterations in conditions caused by CD8 T-cell reductions.
Thanks.

REFEREE: Associate Editor | **Revision** (0) 10 Jun 2020

Dear EIC,
Based on reviewer comments this manuscript needs some corrections.
Regards

REFEREE: EIC | **Revision** (0) 10 Jun 2020

Dear Author,
The reviewers' comments are mentioned. Please correct the details as mentioned above carefully according to reviewers' request.
Thanks.

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Dear Prof. Farnand Imani,

First, I would like to thank you for your answer and for your availability for a possible publication of our article on Anesthesiology and Pain Medicine. The undersigned and the other authors are certainly available to carry out the major revision as required.

Regarding the comments of the reviewer 2 we appreciate the advice not to be verbose into the description of the patient's pain history and the technical notes of the implant. We will certainly do this with these improvements.

Regarding the comments of reviewer 1, although we do not agree with his theory, we cannot understand how it is possible to revise the manuscript unless we withdraw it. By way of clarification we would like to give further details to support our hypothesis.

Several times the reviewer states that it cannot be proven that Tocilizumab could not have been the cause of pocket inflammation. I believe there was a misunderstanding. In fact, we do not claim that Tocilizumab caused inflammation but on the contrary that it helped to heal. Regardless of the cause of the inflammation, which cannot be demonstrated without a biopsy, the cytokine storm from COVID-19 would have had far more serious causes if the citokine storm had not been contrasted with Tocilizumab. We believe that a high systemic inflammatory tone due to COVID-19 had an off-target effect on the IPG pocket site Furthermore, our hypothesis is that this event occurred after some time due to the tissue adjustments due to the scar[1].

For all these reasons we have never considered Tocilizumab to be the cause of the inflammatory reaction but, on the contrary, to be the cause of healing; the meaning of all this is reported in the last sentence of the discussion: "*We are also evaluating the administration of Tocilizumab in future patients with aggressive IL-6/174 polymorphism and post-surgical hyperimmune reaction*".

1. Nishimoto N, Yoshizaki K, Tagoh H,Monden M, Kishimoto S, Hirano T, Kishimoto T. Elevation of serum interleukin 6 prior to acute phase proteins on the inflammation by surgical operation. Clin Immunol Immunopathol. 1989; 50: 399–401.

Kind Regards

Alfonso Papa, MD

OPEN PEER REVIEW

Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (1) — 18 Jul 2020

Dear AE,
Thank you for inviting me again to review the revised manuscript ID#104151. I read by interest this revised manuscript, and fortunately, author could reply to majority of questions
Sincerely

REFEREE: Associate Editor | **Revision** (1) — 18 Jul 2020

Dear EIC,
Based on reviewers' comments the majority of requested items were corrected.
Final decision: Acceptance
Regards

REFEREE: EIC | **Revision** (1) — 18 Jul 2020

Dear Author,
The document is reviewed carefully by the reviewers. According to their comments and your revisions as requested, this manuscript is accepted.
Thanks.