Author's response to reviews

Title: Immunohistochemical localization of urokinase-type plasminogen activator, urokinase type plasminogen activator receptor, and alpha2-antiplasmin in human corneal perforation: a case report

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Author's response to reviews:

Editor-in-Chief
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Re: MS: 2357038507481614

Immunohistochemical localization of urokinase-type plasminogen activator, urokinase type plasminogen activator receptor, and alpha2-antiplasmin in human corneal perforation: a case report

Dear Editor-in-Chief,

It is a pleasure to communicate with you again in relation to the peer revision of our above titled manuscript. First of all, I would like to thank the editor, and the reviewers with whose comments the scientific value of this paper increased immensely. I feel indebted to you all for your time and efforts to increase the scientific value of this paper. Please note the following changes made to the manuscript in accordance with the reviewers’ comments.

We believe that we have answered all reviewers’ questions in a satisfactory manner and that the paper will make an important and timely contribution to your journal.

Responses to Reviewer 1

Minor points
1. There are some redundant information which could be avoided (e.g. Background: “from ulcer of no clear causes.” and Case presentation: “The cause of her corneal ulcer was unknown.”).

As suggested by reviewer 1, we have modified these sentences in order to avoid such redundant information (page 4, lines 16-18, page 5, lines 10-12).

2. For the benefit of readers, who are not very familiar with CD68 or alpha-SMA, some more information about these factors should be given.

As suggested by reviewer 1, we added information about CD68 and alpha-SMA in the revised manuscript (page 6, lines 5-7).

Responses to Reviewer 2

1. P5 More details of the case are needed-For example: Time line of development of the ulcer and presence of “hot tears”. Is there any systemic underlying pathology that could have contributed to the development of the ulcer? The case would have been of more interest if the cause of her ulceration was known based on her “continued steroid and antibiotic eye drops in her right eye for approximately 15 years”. Was there a fungal infection? A parasitic infection? Can any organisms be found in the tissues?

In response to the comments by reviewer 2, we have altered phrases describing the details of the case to more clearly convey clinical history (page 5, lines 3-6, 9-12).

2. P8, L 3: To accurately say that a cornea is fibrotic, either a better photo of the cornea or immunohistochemistry for biomarkers needs to be carried out.

As requested by reviewer 2, a photograph (Fig. 1B) was added to Fig. 1.

3. P8, L6: “both neutrophils and corneal fibroblasts migrated in the stroma near the corneal ulcer”. At the magnification and quality of Figure 2, the identity of the inflammatory cells cannot be determined. They probably are neutrophils and corneal fibroblasts but enlarged cells as insets need to be added to better identify the presence of neutrophils. Can monocytes/macrophages be identified in the cornea?

We agree with the reviewer’s suggestion. We have modified the composite photographs in Fig.2 accordingly.

4. CD68 is found on both macrophages and monocytes. The authors refer to the cells that stain with the antibody to CD68 as macrophages. This is probably true but the authors need to establish this identity.

It is true that CD68 is found on both macrophages and monocytes. We added information regarding this point (page 6, lines 5-6). We also changed the
description about “macrophages” to “CD68 positive cells” in the manuscript.

Minor revision

1. The English needs to be checked. In almost every sentence there is a problem with grammar.

The revised manuscript has been carefully reviewed by an experienced medical editor whose first language is English.

2. The description of the case in the Abstract should be revised for readability.

We have rewritten the Abstract section.

3. The identification of uPAR and uPA and their colocalization on monocytes and macrophages has been well studied. In addition, full length active uPAR is probably not present on myofibroblasts (Bernstein, Mount Sinai School of Medicine). The antibody used in this study probably is Abcam ab103791 which is made to a C-terminal peptide present both on the intact and on the cleaved form of the receptor. The import of this is not addressed in the paper.

This suggestion is indeed very valuable advice. We have added sentences regarding the relationship between uPAR cleavage and corneal myofibroblasts in the Conclusion section (page 11, lines 4-9). One reference was added (Bernstein et al 2007, reference no.14). We also provided detailed information on the antibody used in this study (page 11, lines 4-9).

4. P10 line 6 “degradation” should be substituted for the older term “melting” when referring to corneal ulceration.

We changed the description of “melting” to “degradation” in the manuscript. (page 11, line 11).

5. P10 L17-18, Please refer to the alpha2AP positive cells as myofibroblasts or alpha-SMA positive fibroblasts.

We changed the description of “corneal fibroblasts” to “alpha-SMA positive fibroblasts” in the manuscript. (page 12, lines 2,3,5).

We thank you, the editor and the reviewers, for the time and effort spent throughout the review process of this manuscript. We believe that the excellent comments provided by all increased the utility of this paper. We hope we were able to revise the paper in accordance with the reviewers’ expectations. Please note that we will remain open to further comments and suggestions from the reviewers. We are honored to be working on this paper with you throughout this revision process.
Sincerely yours

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