Author's response to reviews

Title: Periodontitis associated with Plasminogen Deficiency: A Case Report

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Author's response to reviews: see over
Re.: Comments to the reviews: Neering et al. “Periodontitis associated with Plasminogen Deficiency: A Case Report”

Dear Prof. Pietruska,

Thank you for the thorough review of our above-stated manuscript. We greatly appreciate the efforts taken by you and by the reviewers.

All suggestions and corrections have been incorporated into the manuscript.

Attached please find the revised manuscript. We would be grateful, if our manuscript could be considered for publication in the “BMC Oral Health”.

Sincerely,

Sarah Neering
Review 1 Atsushi Saito

Major critiques

Reviewer’s comment: The results of full-mouth periodontal examination should be presented as figure charts.

Author’s answer: The authors have included the Florida Probe charts of the patient at Baseline, reevaluation, 12 month and two years following non-surgical periodontal therapy and at the end of observation period.

Reviewer’s comment: Rather than presenting many oral photographs, the authors should present the radiograph taken at the time of reevaluation following active periodontal therapy (full-mouth SRP+adjunctive antimicrobial therapy).

Author’s answer: The authors have included additional panoramic x-rays (before therapy and 3.5 years following SRP).

Reviewer’s comment: Please provide the diagnosis of periodontitis according to an appropriate periodontal disease classification.

Author’s answer: The authors adhere to the current classification of periodontal diseases (Armitage, 1999) and classified the presented case accordingly as „periodontitis modified by systemic factors“.

Page 4 line 4 to line 7 from above. The sentence „The present case report presents the treatment of a female patient with periodontitis associated with type I PLG deficiency using a full-mouth disinfection approach in combination with specific adjunctive systemic antibiotic therapy aimed at altering the oral microbiome.“ has been changed to „The present case report presents the treatment of a female patient with a severe, generalized periodontitis modified by systemic factors (type I PLG deficiency) using a full-mouth disinfection approach in combination with specific adjunctive
systemic antibiotic therapy aimed at altering the oral microbiome."

Reviewer’s comment: Please provide the rationale for introducing this particular adjunctive antimicrobial treatment. Moreover, what was the rationale for selecting full-mouth disinfection? No discussion regarding this is provided.

Author’s answer: The authors agree to the reviewer’s critique and have included the following paragraph in the Discussion section page 6 line 16 to page 7 line 1 from above:

"Therefore, the reduction of the bacterial load by an adjunctive systemic antibiotic therapy may be considered a suitable therapy strategy to further decrease the inflammation and thus the progression of the disease. It is well known that biofilm bacteria show much greater resistance to antibiotics than their free-living counterparts. One potential reason for this increased resistance is the penetration barrier that biofilms present to antimicrobials. A complete disruption of the intraoral biofilm within a short period of time is therefore a prerequisite for the best possible antibiotic efficacy. For that reason the applied therapy approach followed the concept of full-mouth disinfection, i.e. a complete supra- and subgingival debridement within 24 h, followed by the adjunctive systemic antibiotic therapy. In addition to that, the full mouth disinfection approach has been shown to drastically reduce periodontal pathogens in patients with generalized aggressive periodontitis, thus potentially further reducing the risk of disease progression. The presented treatment strategy is further supported by the guidelines of the American Academy of Periodontics as well as the German Society for Periodontology that recommend the use of a systemic adjunctive antibiotic therapy in patients with aggressive periodontitis.

Reviewer’s comment: This section is poorly organized. The authors failed to discuss the findings from the present study in relation to other studies.
For example, how and why the authors perceive that treatment outcome of this particular case was superior? To those reported by others?

The authors appreciate this valuable comment and have included the following information page 7, line 2 to line 20 from above:

“Only a limited number of cases with plasminogen deficiency and oral lesions have been reported in the literature (Sivolella, De Biagi et al. 2012). Several therapeutic approaches have been described (Suresh, Aguirre et al. 2003; Baykul and Bozkurt 2004; Tefs, Gueorguieva et al. 2006; Kurtulus, Gokbuget et al. 2007, Silva, Bariani et al. 2006; Toker, Toker et al. 2007) including scaling and root planning, chlorhexidine rinsing, administration of antibiotics (Kurtulus, Gokbuget et al. 2007; Mehta and Shapiro 2008) and periodontal surgery. These case reports, however, lack detailed information of the rendered dental therapy and the intraoral colonization with periodontal pathogens. Those very few reports about the adjunctive use of antibiotics do neither mention the type of antibiotic nor the duration of its intake, and its association to any additional periodontal treatment (Gunhan, Gunhan et al. 1999; Baykul and Bozkurt 2004), thus precluding the validation of an adjunctive systemic antibiotic therapy. Most of the above mentioned reports have been described as failures due to rapid gingival regrowth and progressive bone loss (Sivolella, De Biagi et al. 2012). Only Silva et al. report about a complete remission of the oral tissue enlargement by applying prednisolone systemically without gingivectomy (Silva, Bariani et al. 2006). However, the patient presented did not suffer from ligneous periodontitis, but from gingival enlargement only. Another case report indicated that the treatment with warfarin exerts protection against relapsing gingival hyperplasia over an observation period of 3 years in a 54 year old patient. The authors reported about a combination of gingivectomy, an administration of 20 mg
doxycycline daily, and the use of a 0.12% chlorhexidine digluconate mouthrinse. One week after surgery the patient started with 5 mg warfarin daily for an indefinite time. Any supportive periodontal therapy is not mentioned.

Reviewer’s comment: Please consider reducing the number of oral photographs. Instead, the authors should present the charts of periodontal examination which indicate PPD, CAL and BOP, etc... Also, post-treatment X-rays should be presented. Otherwise, no evidence of the improvement in periodontal condition can be discussed.

Author’s answer: The authors agree and have already addressed these critiques in response #1 and #2 (please see above)

Minor critiques

Reviewer’s comment: Abstract This section should be structured into the following three sections: Background, Case presentation and Conclusion. p3 L16 “The reported therapy has significantly improved periodontal health...” Please provide information regarding when this reevaluation was performed after “the reported therapy.” p3 L23 “...and progressive attachment loss.” No description regarding the attachment loss or bone resorption was provided in “Case report (should be Case presentation)” section. p3 L25 “...and a strict supportive periodontal therapy regime (regimen?) “ No description regarding supportive periodontal therapy is provided in “Case report” section of the Abstract.

Author’s answer: The authors agree and have modified the manuscript accordingly in order to overcome the objections.

Reviewer’s comment: Background
This section is poorly organized. The authors should briefly describe plasminogen deficiency and its effect on the periodontal tissue, before introducing the present case. Also, appropriate reference should be given to such additional information.

p4 L5 “A patient with generalized aggressive periodontitis...”
It is unclear which patient this is. Please consider using “In this case report...”

p4 L10 “Plasminogen seems to play an important...”
This notion should be placed before the previous sentence regarding the efficacy of the treatment.

Author’s answer: The authors agree and rearranged the background. Prior introduction of „case presentation“ replaced the background.

Reviewer’s comment:

Case presentation
p5 L19 “…associated with plasminogen deficiency...”
Should be “…associated with PLG deficiency...”

p5 L19 “…surgical and non-surgical periodontal therapy alone...” It is unclear what this “alone” means. If alone is also associated with “surgical”, does this mean that no non-surgical periodontal therapy was provided before “surgical” therapy?

p5 L22 “However, these treatments have failed...”
Please provide the reference to support this statement regarding treatment failure.

Author’s answer: The authors have included following paragraph:

Treatment approaches for periodontitis associated with PLG deficiency included surgical and non-surgical periodontal therapy. Periodontal surgery without previous supra- and subgingival debridement appeared initially promising, but eventually resulted in pseudomembrane regrowth. Periodontal non-surgical treatment alone i.e. without periodontal surgery or in combination with chlorhexidine mouth rinses, topical administration of plasminogen or heparin, or administration of systemic antibiotics, have been described. However, these
treatments have failed to arrest periodontal disease progression in subjects with type I PLG deficiency.

Reviewer’s comment: Case report
p6 L7 “Class 3 mobility”
Please indicate the index for this.

Author’s answer:

Reviewer’s comment: p6 L27 “A microbiological analysis...”
The methodology regarding the microbiological analysis should be provided in more detail.

Author’s answer: A microbiological analysis of supra- and subgingival plaque revealed the intraoral presence of *Porphyromonas gingivalis*, *Eikenella corrodens*, *Prevotella intermedia*, *Prevotella nigrescens*, *Tannerella forsythensis*, and *Treponema denticola*. *Aggregatibacter actinomycetemcomitans* was not detected. A combined sample of supra- and subgingival plaque before non-surgical periodontal therapy was taken from the deepest periodontal pocket in each sextant and microbial species were detected by polymerase chain reaction (PCR).

Reviewer’s comment: p7 L12 “...signs of arrested periodontitis (Fig. 5).”
In my view, an oral photograph does not indicate the arrest of periodontitis. Instead, the authors should consider providing the radiographic information.

Author’s answer: The authors have attached the corresponding clinical charts.

Reviewer’s comment: Discussion
p7 L9 “...PPD and BOP were markedly reduced...”
This is rather a subjective statement. Please provide the data.

Author’s answer: The authors have attached corresponding clinical charts.
Reviewer’s comment: p7 L22 “However, in vitro data and...periodontal destruction.”
Please indicate the references to support this statement.
p7 L24 “Local extracellular...wound healing.”
Please provide the reference(s) to support this notion.
p8 L10 – p9 L13
Please consider reorganizing these paragraphs. The authors merely introduced findings from other studies and failed to discuss the findings from the present study in relation to these studies.

Author’s answer: The exact pathophysiology of ligneous periodontitis remains, however, unclear. *In vitro* data and animal studies indicated that alterations in tissue repair and host defense mechanisms are responsible for the onset and the progression of periodontal destruction. Local extracellular fibrinolysis by plasmin is required for the initial removal of the fibrin-rich matrix as well as for the remodeling of the granulation tissue and completion of wound healing.

Reviewer’s comment: References
Please refer to the author guideline for appropriate format for presenting references (including the use of capitalization, abbreviation of the journal names, etc...) and revise the list extensively.

Author’s answer: The references have been adapted to the BMC Oral Health reference format

Reviewer’s comment: Figure legends
Figure 7 “direct restauration” should be “direct restoration”?

Author’s answer: The error has been corrected.

Reviewer’s comment: Declaration of competing interests: „I declare that I have no competing interests“

Author’s answer: The remark has been added.
Review 2 Ewa Dolinska

Major compulsory revisions: none
Minor essential revision: none

Discretionary revisions:

Reviewer’s comment: Case report, page 7, lines 14-16
It is written that clinical signs of type I plasminogen deficiency in
the ear, urogenital system, respiratory tract and the eyes
diminished after periodontal therapy. It suggests direct impact of
periodontal therapy on the other regions of the body. Probably it
would be better to write that the positive changes were
observed at the same time. It is not sure what caused those
changes in other than oral cavity regions.

Author’s answer: The recommendation has been adopted.
„Interestingly, the clinical signs of type I PLG deficiency at the
ear, urogenital tract and upper respiratory tract and the eyes
showed positive changes at the same time following periodontal
therapy.“

Reviewer’s comment: Case report, page 7, line 15
after word urogenital probably missing word (system or
mucosa)

Author’s answer: The error has been corrected. „Interestingly, the clinical signs of
type I PLG deficiency at the ear, urogenital tract and upper
respiratory tract and the eyes showed positive changes at the
same time following periodontal therapy.“

Reviewer’s comment: Case report, page 7, line 14
spelling Type I- type I

Author’s answer: The spelling error has been corrected.

Reviewer’s comment: Declaration of competing interests: „I declare that I have no
competing interests“
Author`s answer: The remark has been added.