

Revisor 1.

- 1. It maybe too long for a case report , there are repetitions of Introduction and Discussion, the history can be shortened.**

We appreciate your comment. We carefully revised the introduction and discussion in order to eliminate repetitive information, to obtain a less extensive manuscript. However, a reviewer of the article requested to emphasize and deepen relevance regarding the following points:

1. Management of Drug induced gingival enlargement
2. Precautions can be taken while administering systemic drugs to prevent gingival enlargement
3. Association between dosage of drug administered and gingival enlargement

Thank you very much for your valuable input.

Revisor 2.

- 1. How would the findings of this case report alter the management of the Drug induced gingival enlargement?**

The management of Gingival enlargement induced by Drug depends on the severity and conditions of the oral pathology, and the systemic conditions of the patient. This article proposes that for the management of this oral entity, two important points must be implemented and emphasized. First, the multidisciplinary management of periodontists with the specialist doctors treating each particular case. Due to the fact that in this clinical case the interconsultation and teamwork of both professionals, both periodontal treatment by stage carried out by the periodontist and the adjustment of the dose of cyclosporine (with respect to the clinical results after the initial phase) by the hematologist, allowed the management, control and follow-up of this oral pathology. Second, the management of gingival enlargement in phases: Initial (oral hygiene motivation, mechanical supragingival plaque control, non-surgical therapy), systemic, corrective and maintenance. Emphasizing the maintenance stage, because if a patient is being treated with a drug, particularly an immunosuppressant, it is important to have regular appointments in which to maintain adequate oral hygiene, frequent monitoring of the progression and/or recurrence of the disease

- 2. What precautions can be taken while administering systemic drugs to prevent gingival enlargement?**

Recent studies revealed that the accumulation of gingival fibroblasts observed in drug-associated gingival hyperplasia resulted from inhibition of apoptosis. It has been reported that the pathogenesis of cyclosporine-induced gingival hyperplasia is associated with up-regulated expression levels of proinflammatory cytokines in saliva i.e., interleukin (IL)-1 α , IL-8, and IL-6.

Various risk factors for GE have been identified. These are plaque control, level of gingival inflammation, extent of periodontal destruction, dose and duration of cyclosporine therapy, plasma and tissue concentrations of cyclosporine and its metabolites, age of the patient, and perhaps the underlying comorbidities.

Although suspending the use of medication in most cyclosporine-induced GE cases is not a viable option, such was the case with the patient in this study. In previous studies, it was reported that maintenance of adequate oral hygiene in humans markedly reduced the severity of cyclosporine-induced gingival hyperplasia. In this study, although a significant reduction in GE was observed after the initial phase, it did not prevent the development of gingival hyperplasia.

3. Was there any conclusion regarding association between dosage of drug administered and gingival enlargement?

Pharmacological treatments cannot be modified in most cases of severe GE, as this would lead to non-control of the systemic disease. In the case of the patient in this study, treatment modification aggravated the medullary aplasia, resulting in reappearance of the lesions after surgical removal, thereby requiring repeated interventions. Evidence suggests that 34% of cases show recurrence during 18 months following periodontal surgery, regardless of medication. In our patient's case, consultation with a hematologist was carried out in a bid to modify the dose of cyclosporine administered, from the initial schedule of one 100-mg capsule three times a day, to one 100-mg capsule every other day. When compared with the initial phase, an important reduction in enlargement was observed. This reveals the importance of adequate multidisciplinary management for GE.

Reviewer 3.

- 1. Gingival hyperplasia due to cyclosporine administration is not new and well-known adverse effect of the drug. Thus, it is unclear what kind of aspects are novel worth publication. Looking at the MS in its current description, it is unclear regarding this issue. If the authors reported some novel findings based on their clinical experiences upon case series, it may be welcome for submission. Unfortunately, this MS would not meet this aspect.**

We appreciate your comments, we agree that gingival enlargement due to cyclosporine administration is not new. We consider that the interdisciplinary management due to the patient's systemic disease, added to the therapeutic approach by phases would be the novel aspects with the objective of obtaining better periodontal results in combination with the systemic considerations, considering your observations, we highlighted these elements in the discussion, which are already previously described. We remain attentive to your comments.