

Answering Reviewers

Revisor 1.

1. Dear the Author, My opinion is that this manuscript is possible for publication Regards, Reviewer

We appreciate your comment. Thank you very much

Revisor 2.

1. I understand that your article is a case series. I suggest you to organise the case presentation in a tabel in order to be more easy to read and understand.

In the present work we will describe three clinical cases of PG, this description is presented in the following tables:

Table 1. Pathological personal history				
	CHIEF COMPLAINTS	HISTORY OF PRESENT ILLNESS	HISTORY OF PAST ILLNESS	PERSONAL AND FAMILY HISTORY
Case 1	A 32-year-old woman presented with a lump on the palate that bled frequently and interfered with chewing.	The patient stated that the lesion appeared approximately 3 months prior to the clinical diagnosis.	Denied	None
Case 2	A 42-year-old woman presented with a bulge near the upper lip. The patient complained of pain when chewing and mobility of the central incisor.	The lesion had 5 months of evolution. It bled on touch, and it had a firmer consistency than before.	Denied	Father was diagnosed with Type 2 Diabetes Mellitus 5 years earlier.
Case 3	A 38-year-old woman had two enlargements which bled frequently and interfered with chewing.	The patient said that the lesion had 6-month evolution period, during which it grew until chewing became an uncomfortable exercise.	Denied	Mother was diagnosed with high bold pressure in 2017.

Table 2. Clinical, imaging and laboratory examinations			
	INTRA-ORAL CLINICAL EXAMINATIONS	IMAGING EXAMINATIONS	LABORATORY EXAMINATIONS
Case 1	Oral examination revealed a localized exophytic lesion manifested as a 25 x 12 mm erythematous mass with smooth consistency which bled on provocation. The lesion was pedicled	Periapical radiography showed horizontal bone loss up to the middle third region of dental organ 22 (Figure 1b).	Hemoglobin level was slightly low (11.8 g/dL). The other results were within normal limits.

	and attached to the marginal gingiva of dental organ 22, and it extended to the middle third of palatal surface of dental organs 21 and 23 (Figure 1a). In addition, dental organ 22 presented grade-three mobility and extensive caries along the palatine surface.		
Case 2	During the oral examination, a semi-ovoid 16 x 10 mm formation of gingival mucosa was found. The surface was smooth and reddish in color. The growth was pedicled and attached to the marginal gingiva of dental organ 21 (Figure 2a). This dental organ presented grade-three mobility, supra- and sub-gingival calculus, and probing depth of 8 mm.	Panoramic radiography showed generalized alveolar bone loss in both arches (Figure 2b).	Neutrophil count was slightly high (72%). However, the levels of the other white cells were within normal limits [platelet level ($309 \times 10^3/\mu\text{L}$) was normal, and hemoglobin level (14.5 g/dL) was normal].
Case 3	During the clinical examination, two reddish exophytic lesions with smooth surfaces were identified. The lesions were about 20 x 15 and 10 x 12 mm in size. They were pedicled and attached to the interproximal zone of dental organs 46 and 47 (Figure 3a). Supra- and sub-gingival calculus were identified in the two dental organs.	Periapical radiography showed interproximal bone loss between dental organs 47 and 48 (Figure 3b); and between dental organs 46 and 47 (Figure 3c).	Hemoglobin, neutrophil and platelet levels were within normal limits.

Table 3. Diagnosis and treatment

	PRESUMPTIVE DIAGNOSIS	MACROSCOPIC DESCRIPTION AND FINAL DIAGNOSIS	TREATMENTS	OUTCOME AND FOLLOW-UP
Case 1	Based on all the information obtained from anamnesis, and from radiographic imaging, clinical features of lesion such as ulcerated surface, bleeding on provocation, as well as the adjacent local irritants, a presumptive diagnosis of pyogenic granuloma was made.	Microscopic examination revealed a segment of buccal mucosa with fibrous stroma and a diffuse lymphoplasmacytic-type inflammatory infiltrate. There was evidence of old and recent stromal hemorrhages around newly-formed, congested blood vessels having irregular contours and varied diameters, with hyperplastic endothelial cells covered by epithelium with extensive areas of erosion. This histological examination	The exophytic lesion was removed with excisional biopsy (Figure 1c). The procedure was performed under local infiltrated anesthesia [2 % mepivacaine with epinephrine ($10 \mu\text{g/mL}$)]. The incision was made with a 15C scalpel blade on the base of the pediculated lesion. The gingival tissues were remodeled with LaGrange scissors. Due to the extent of bone loss, degree of mobility, and the extensive caries in dental organ 22, a decision was made to remove it (Figure 1d). Oral prophylaxis was performed with an ultrasonic device and Gracey 1-2 curettes in order to remove the local irritants on the adjacent teeth. After the procedures, 500-mg amoxicillin	After three months of follow-up, the scarring was satisfactory, and there was no recurrence.

		confirmed the diagnosis of pyogenic granuloma (Figures 1e and 1f).	tablets were prescribed for the patient, to be taken 3 times daily for 5 days, and post-surgery indications were given.	
Case 2	The information obtained from the clinical, radiographic examination, and the history of evolution of the lesion led to a presumptive diagnosis of pyogenic granuloma.	Histological analysis revealed a segment of mucosal stratified squamous epithelium with underlying fibrovascular stroma and a dense infiltrate of chronic inflammatory cells, stromal hemorrhage, large number of budding capillaries, fibroblasts, and areas of extravasated blood. Therefore, the diagnosis of pyogenic granuloma with gingival hyperplasia was confirmed (Figure 2e). Along with this final diagnosis, and based on the results of intraoral clinical examination, periodontal chart, and X-ray, a stage III grade generalized periodontitis was also diagnosed.	The exophytic mass was removed through an excisional biopsy (Figure 2c), along with the extraction of dental organ 21. The extraction was performed without complications (Figure 2d). The procedure was performed under local infiltrated anesthesia [2 % mepivacaine with epinephrine (10 µg/mL)]. The incision was made with a 15C scalpel blade on the base of the pediculated lesion. Oral prophylaxis was also performed with ultrasonic device and McCall 13-14 and 17-18 curettes. After the procedures, amoxicillin tablets (500 mg) were administered to the patient 3 times daily for 5 days, and post-surgery indications were given.	The scarring was satisfactory after three months of follow up, and there was no recurrence. Additional therapy was started for the periodontitis.
Case 3	Based on all the information obtained during the clinical and radiographic examinations, as well as the clinical features of the lesion, and the adjacent local irritants, the presumptive diagnosis was pyogenic granuloma.	On microscopic examination, sections showed stratified squamous epithelium with non-neoplastic endothelial cell proliferation, formation of new blood cells, as well as acute and chronic inflammatory cell infiltration in a collagenous matrix around the newly formed, congested blood vessels with irregular contours and varied diameters. The blood vessels were covered by epithelium with extensive areas of erosion. These features corroborated the presumptive diagnosis of pyogenic granuloma (Figures 3e and 3f).	An excisional biopsy was performed under local infiltrated anesthesia [2 % mepivacaine with epinephrine (10 µg/mL)]. The incision was made with a 15C scalpel blade on the base of the lesion. The incision was extended to the periosteum, and a 2-mm margin was included from the adjacent soft tissues (Figure 3d). Oral prophylaxis was performed with an ultrasonic device and McCall 17-18 curettes in order to remove the calculus on dental organs 46, 47 and 48. Post-surgery indications were given, and the patient was placed on 500 mg tablets of amoxicillin 3 times daily for 5 days.	After three months of follow-up, the scarring was satisfactory, and there was no recurrence.

2. Please explain if there are new information in this cases. Please expin the novelty!

After six months of follow-up, the scarring was satisfactory, and there was no recurrence.

In all three clinical cases described, bone tissue loss is observed and, although infrequent, PG can cause significant bone loss on rare occasions. Therefore, we suggest that bone loss should be considered as a possible diagnostic feature of PG, notwithstanding the fact that the lesion arises from soft tissues.

3. In the discussion section is mandatory to compare your cases with the existing literature.

PG is considered a reactive self-limited pathology that presents as an exuberant proliferation of connective tissue in response to stimulation by some local irritant factor. Tripathi et al., [8] and Verma et al., [9] concluded, in their clinical case reports, that poor oral hygiene leading to abundant biofilm and dental calculus accumulation causes chronic irritation and contributes to the development of oral PG, similar to the cases presented. In the third case the presence of supra and sub gingival calculus was identified in the dental organs, which could be associated with the appearance of PG, and the periapical radiograph showed interproximal bone loss. However, in the first clinical case, we reported the presence and extent of dental caries in dental organ 12. Dental caries is caused by etiologic agents, such as Staphylococci and Streptococcus which produce colonies with fungal characteristics [15]. Chronic trauma provides a pathway for invasion of these microorganisms that induce proliferation of vascular connective tissue. Thus, it can be inferred that these pathogens also act as stimuli that favour the formation and growth of pyogenic granuloma [1,16].

Most researchers have reported that radiographic evaluation of pyogenic granuloma does not show relevant features because the lesion arises from soft tissues [1,18,19,20]. However, pyogenic granuloma is a benign inflammatory lesion that expresses significantly more vascular endothelial growth factors and basic fibroblast growth factors than healthy gingiva and periodontitis [21]. In all three clinical cases described, bone tissue loss is observed and, although infrequent, PG can cause significant bone loss on rare occasions, as reported by Mastammanavar et al.,[7], Tripathi et al.,[8] and Verna et al., [9].