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CASE REPORT

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Role of histopathology in the management of the gingival enlargement in a patient on antihypertensive therapy based on calcium channel blockers: a case report

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Abstract

Periodontal pathology is often represented by increases in gingival volume, with pronounced inflammatory phenomena. These manifestations require a more accurate diagnosis and knowledge of the etiopathogenic factors involved. The periodontal treatment applied must be related with the etiopathogenic circumstances. Periodontal disease sometimes has a complex appearance, with intertwined local and systemic favorable factors that make it difficult to include it in a certain taxonomic form. Also, in general, the adult patients have associated chronic diseases that involve the administration of several drugs, which induce on long-term both therapeutic and side effects. Furthermore, diseases in the oral cavity may occur frequently, which require complex and associated dental and periodontal treatment, also occlusal rebalancing, which is a real interdisciplinary challenge. In this case report, periodontal status is determined by a combination of local and systemic favorable factors. However, the histopathological analysis of the gingival samples revealed inflammation without characteristic fibrous hyperplasia changes of the Amlodipine calcium channel blocker (CCB) administration, the antihypertensive medication of the patient. Thus, Amlodipine does not have a hyperplasic effect on gingival mucosa in all cases. Therefore, even if they are more expensive, investigations must be complex, if necessary, in establishing the involvement of the side effect of the systemic medication in periodontal pathological changes. CCB systemic medication is essential, even vital, for maintain the arterial pressure at normal values, should not be altered without the real indication and to the recommendation from a specialist doctor, and the periodontal treatment must be focused to eliminate the local factors.

Keywords: periodontal disease, gingival overgrowth, histopathological changes, calcium channel blockers, treatment.

Introduction

Periodontal disease has been studied for decades and there has been great progress in establishing etiopathogenic mechanisms and expanding the treatment possibilities. It is known to be an infectious disease and several species of bacteria have been associated with this condition. However, the presence of these bacteria cannot entirely explain all the disease's features. The host's influence is considered of higher importance and could modify and modulate the clinical response of the periodontal disease [1].

The latest data place periodontal disease on the 6th place as a global prevalence, the forms of severe periodontitis having a prevalence of 11%, ahead of cardiovascular diseases estimated at 6.6% [2].

Gingival overgrowth (former "gingival hyperplasia") is characterized by an accumulation of extracellular matrix (ECM) in the gingival connective tissue [3], increasing the number of cells and fibrillar elements. This has been associated with several factors including systemic inflammation, side effects of some drugs and cardiovascular diseases [4].

Cardiovascular diseases have a notable occurrence rate in the developed countries, having a major impact on the body. Blood vessel disorders, arterial hypertension and atherosclerosis are now the leading causes of death in western countries. Thus, it is not surprising that this group of diseases may have an impact on the gingival tissue and the installation of periodontal disease [5]. Clinically, the increased gingival volume is the most common gingival change in cardiovascular diseases [6].

On the other hand, the treatment used in the control of hypertension can exhibit gingival histopathological (HP) changes. It is known that drug-induced increases in gingival volume occur primarily as a common side effect in these classes of drugs: (*i*) calcium channel blockers (CCBs) (Nifedipine, Diltiazem, Amlodipine and Verapamil) [7–10]; (*ii*) antiepileptic drugs (Phenytoin) [11]; (*iii*) immunosuppressant drugs (Cyclosporine) [12].

Drug-induced gingival overgrowth usually occurs within the first three months of the treatment, and it commence is characterized by an increase in the interdental papilla's volume [9].

Thus, the periodontist must consider three aspects when treating a patient with cardiovascular disease: (*i*) the effect of drugs on the periodontium; (*ii*) the risk of infectious endocarditis following periodontal procedures; (*iii*) the possibility that periodontal disease may have contributed to the cardiovascular disease.

Aim

This case report presents the gingival clinicopathological changes in a patient with antihypertensive medication

represented by Amlodipine (CCB), HP analysis to establish the changes determined by this systemic treatment for an adequate local periodontal treatment.

Case presentation

A 64-year-old male patient experiences gingival volume enlargement accompanied by spontaneous gingival bleeding. His medical background revealed dust allergy and arterial hypertension that has been under treatment for three months with an Amlodipine CCB associated with an inhibitor of the angiotensin system, and a minor cerebral stroke in 2020. Other drugs administered: Aspirin and statins.

During the intraoral clinical examination, generalized gingival volume increases were observed having color changes on bright red on the maxillary and purple on the mandible, with granular appearance at the free gingival margin level and firm consistency on probing (Figure 1). Both the plaque index and bleeding index were 100%, while the presence of subgingival calculus could be observed on 21.87% of the dental surfaces. Other local factors were the total metalo-ceramic restoration, with mixed support, dental and 2.6 implant, which restore the edentation of 1.7, 2.3, 2.5 teeth, with the coronary fracture of the implant and of the 2.2, 2.4 teeth pillars. On the mandible could be also observed a total metalo-ceramic bridge from the 3.6 implant to the 4.7 molar, which restore the edentation of the 4.6, 4.5, 3.4, 3.5 teeth. The occlusal analysis showed a chronic occlusal trauma. The radiological exam (Figure 2) revealed vertical resorptions located at the central interincisive septum level on the mandible and maxillary, and to the 2.4 tooth. Also, around 2.6 implant was observed peri-implant resorption. The periodontal diagnosis was gingival hyperplasia on the background of adult periodontitis and peri-implantitis. After the new classification of the *American Academy of Periodontology* (AAP) and the *European Federation of Periodontology* (EFP) [13], the diagnosis was stage III C periodontitis and 2.6 peri-implantitis.

Histopathological features

HP examination was required to assess gingival changes and determine their nature. After scaling, ablation of the prosthetic restorations and rinsing with mouthwash with 0.2% Chlorhexidine, twice daily for 14 days (Figure 3), the excisions of the overgrowth papillae from the frontal area 1.3, 1.2, 1.1 were performed with a 15C blade scalpel.

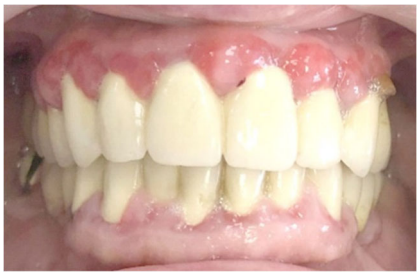

Figure 1 – ***Clinical aspect at presentation of the patient with signs of inflammation of the periodontium, with increases in gingival volume and color changes.***

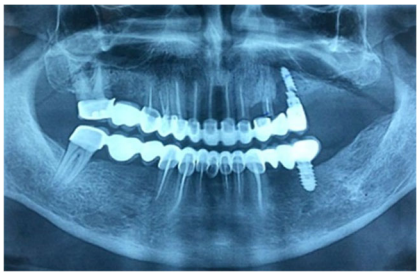

Figure 2 – ***Radiological aspect at presentation of the patient with generalized bone resorption.***

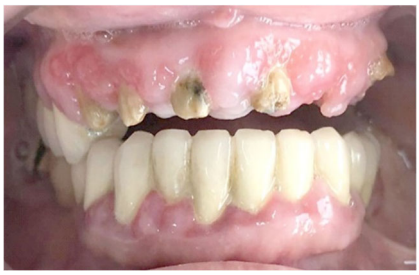

Figure 3 – ***Clinical aspect after ablation of the prosthetic restoration, with an improvement in the clinical appearance of the periodontium but still with increases in gingival volume and color changes.***

For the comparison of HP changes, a control tissue was selected. There was used an inflammatory papilla excised with a 15C blade scalpel from the area of the 2.8 last molar of a young patient, non-smoker, without any associated diseases or under treatment.

The collected anatomical pieces were sent to the Laboratory of Pathology for examination.

The tissue fragments were fixed in 10% buffered formalin for 36–40 hours; further on, they were routinely HP processed using a Leica ASP200 S tissue processor (90 minutes ethanol 70° heated at 40°C, 105 minutes ethanol 80° heated at 40°C, 105 minutes ethanol 96° heated at 40°C, 60 minutes ethanol 100° heated at 40°C, 90 minutes ethanol 100° heated at 40°C, 90 minutes ethanol 100° heated at 40°C, 120 minutes xylene heated at 52°C three times, 60 minutes paraffin heated at 58°C, 120 minutes paraffin heated at 58°C, 180 minutes paraffin heated at 58°C). Paraffin blocks were embedded using a HistoCore Arcadia Embedding Center and cut using a Leica RM2265 rotary microtome in 3 µm thick sections.

Routine Hematoxylin–Eosin (HE) and immunohistochemical (IHC) tests were performed on BOND-III IHC/ISH automatic staining system for clusters of differentiation CD3, CD5, CD20, CD79a, CD138, CD68, and p53, using BOND Polymer Refine Detection kit.

Details for IHC markers performed: anti-CD3 (clone LN10, Leica, Nussloch, Germany), mouse, heat-induced epitope retrieval (HIER) pretreatment in ethylenediaminetetraacetic acid (EDTA), pH 8, ready-to-use (RTU); anti-CD5 (clone 4C7, Leica, Nussloch, Germany), mouse, HIER pretreatment in EDTA, pH 8, RTU; anti-CD20 (clone L26, Leica, Nussloch, Germany), mouse, HIER pretreatment in citrate buffer, pH 6, RTU; anti-CD79a (clone CD79a, Leica, Nussloch, Germany), mouse, HIER pretreatment in citrate buffer, pH 6, 1:50 dilution; anti-CD138 (clone Mi15, Leica, Nussloch, Germany), mouse, HIER pretreatment in citrate buffer, pH 6, RTU; anti-CD68 (clone 514H12, Leica, Nussloch, Germany), mouse, HIER pretreatment in EDTA, pH 8, RTU; anti-p53 (clone DO7, Leica, Nussloch, Germany), mouse, HIER pretreatment in EDTA, pH 8, RTU.

All the slides (both HE and IHC stainings) were analyzed on an Olympus BX41 microscope. The presence of CD3, CD5, CD20, CD79a, CD138 and CD68-positive cells was semi-quantitatively evaluated: absent, few cells, numerous cells both in *lamina propria* and intraepithelial.

The patient presented marked epithelial hyperplasia, with acanthosis and papillomatosis; marked diffuse spongiosis was present within the epithelium; within the *lamina propria*, marked chronic inflammatory infiltrate was present, consisting of mononuclear cells (lymphocytes and monocytes and numerous plasma cells, some of them with intracytoplasmic hyaline globules – Russell's bodies), with mild focal lymphocytic exocytosis within the epithelium; no neutrophils or eosinophils were identified; thick collagen bundles with mild fibroblastic proliferation were present (Figure 4, A–F). The inflammatory infiltrate immunophenotype revealed presence of numerous T-lymphocytes (CD3+, CD5+) admixed with very few B-lymphocytes (CD20+, CD79a+) and very numerous CD138+ cells (plasma cells) and few CD68+ cells (histiocytes) within the *lamina propria*. The intraepithelial exocytosis of inflammatory cells consisted exclusively of T-cells (CD3+ and CD5+), no B-cells, plasma cells or histiocytes being present (CD20-, CD79a-, CD68- within the epithelium; CD138 presented membranous epithelial positivity without revealing any nonepithelial positive cells interspersed between the epithelial cells) (Figures 5–7). No neutrophils or eosinophils were present within the inflammatory infiltrate. p53 was negative (Figure 8, A and B).

Control gingival mucosa presented epithelium with mild acanthosis without spongiosis; very few lymphocytes were present within the *lamina propria* consisting exclusively of T-cells (CD3+, CD5+) and histiocytes (CD68+); no B-cells (CD20-, CD79a-), plasma cells (CD138-), eosinophils or neutrophils were identified in *lamina propria*. Interestingly, despite the apparent lack of lymphocytic exocytosis within the epithelium, IHC tests identified few T-lymphocytes (CD3+, CD5+) within the epithelium, in similar proportion as the studied case. Also, no B-cells, plasma cells or histiocytes are present within the epithelium (CD20-, CD79a-, CD68- within the epithelium; CD138 presented membranous epithelial positivity without revealing any non-epithelial positive cells interspersed between the epithelial cells) (Figures 4–7). As expected, p53 (oncogene product) was negative (Figure 8, A and B).

Discussions

Diseases of the periodontium have at times a complex aspect, with intertwined local and systemic favorable factors that makes difficult the inclusion in a certain taxonomic form. In general, adult patients exhibit both associated chronic diseases, with multiple long-term medication, and long-term side effects. Furthermore, diseases in the dental cavity may occur frequently, which involves complex and associated treatment dental and periodontal, also occlusal rebalancing, which is a real interdisciplinary challenge.

Drug-related periodontal pathology is well known, the treatment of cardiovascular diseases being frequently associated with gingival enlargement. These therapies stem from classes of antihypertensives, antiarrhythmics, vasodilators, anticoagulants, antiplatelet drugs, and lipid-regulating drugs [5].

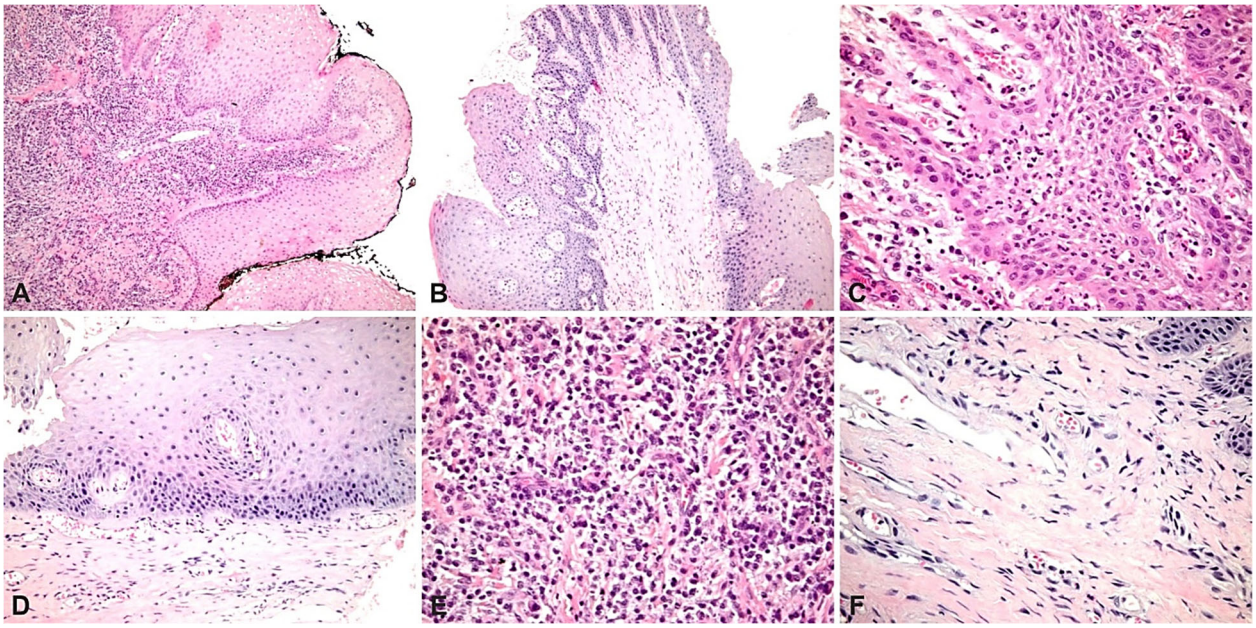

Figure 4 – ***Histopathological aspect of the gingival mucosa: (A) Epithelial hyperplasia with marked acanthosis and papillomatosis; mild hyperplasia of the basal cells; abundant cytoplasm with focal clearings of the superficial spinous cells (glycogen); marked chronic inflammatory infiltrate within the lamina propria; focal vascular dilatation; (B) Control – gingival mucosa with mild acanthosis; apparent thickening of the epithelium due to tangential cut; very few lymphocytes within lamina propria (normal histological findings); no vascular dilatation; (C) Marked spongiosis with significant lymphocytic exocytosis within the epithelium; numerous lymphocytes and plasma cells present within the lamina propria; vascular dilatation; (D) Control – no spongiosis and no obvious lymphocytic exocytosis within the epithelium; few dilated blood vessels with several non-agglutinated red blood cells with normal cytoplasmic staining (no pathological significance); (E) Marked inflammatory infiltrate consisting in lymphocytes and very numerous plasma cells within the lamina propria; occasional hyaline globules within the plasma cells cytoplasm – Russell's bodies; collagen deposition in thick bundles with mild fibroblastic proliferation; (F) Control – lamina propria consisting of collagenous background with fibrocytes, few small, dilated capillaries and very few lymphocytes (normal histological findings); no plasma cells are present. Hematoxylin–Eosin (HE) staining: (A and B) ×200; (C–F) ×400.***

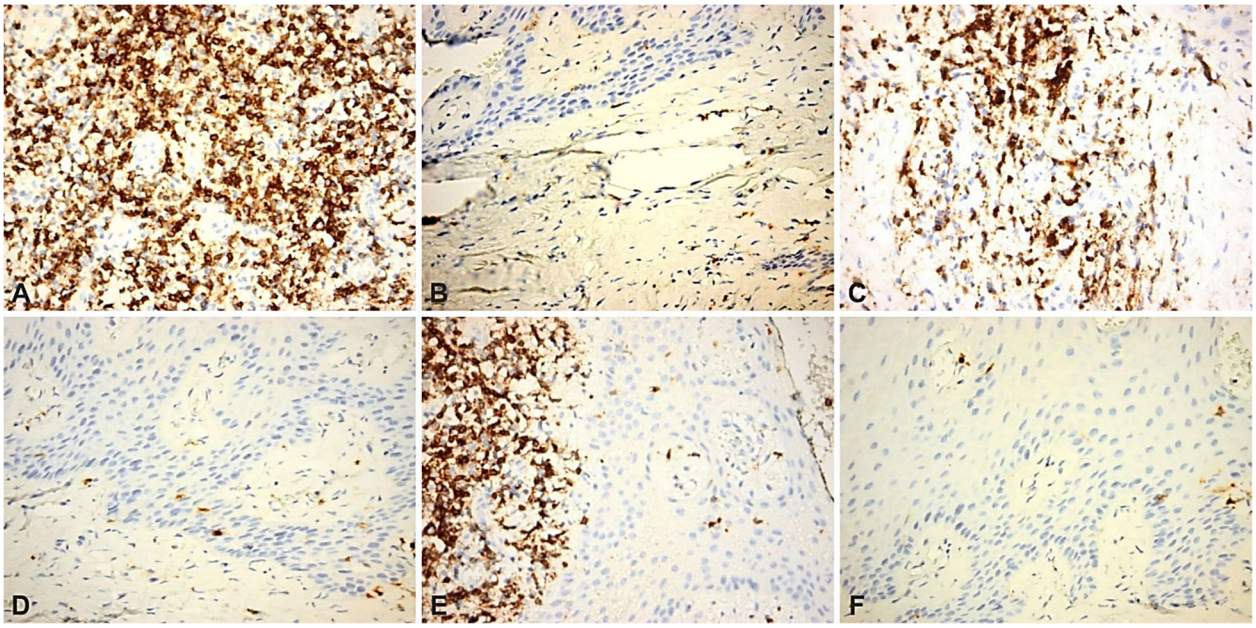

Figure 5 – ***T-lymphocytes distribution within the gingival mucosa: (A) Numerous CD3+ T-lymphocytes within the inflammatory infiltrate; very few negative lymphocytes are present; blood vessels are negative; (B) Control – few CD3+ T-lymphocytes within the lamina propria (normal histological findings); (C) Numerous CD5+ T-lymphocytes within the inflammatory infiltrate; very few negative lymphocytes are identifiable; the density of the inflammatory infiltrate is lower than in Figure 5A, however the proportion of the CD5+ cells is similar; (D) Control – few CD5+ T-lymphocytes within the lamina propria; occasional T-cell intraepithelial exocytosis; no spongiosis is present (normal histological findings); (E) Numerous CD5+ T-lymphocytes within the inflammatory infiltrate, with occasional intraepithelial exocytosis; very few negative lymphocytes are present, with similar density of the inflammatory infiltrate and proportion of the CD5+ cells to Figure 5A; (F) Control – CD5+ T-lymphocytes within the squamous epithelium; no spongiosis is identifiable (normal histological findings). Anti-CD3 antibody immunomarking: (A and B) ×400. Anti-CD5 antibody immunomarking: (C–F) ×400. CD: Cluster of differentiation.***

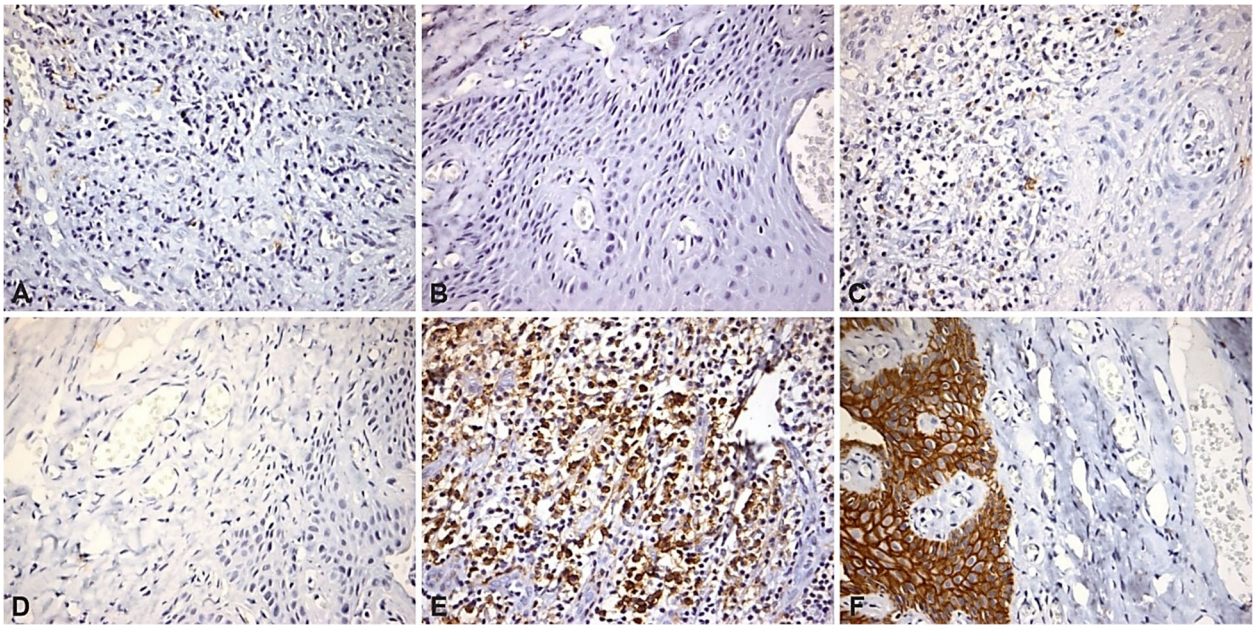

Figure 6 – ***B-lymphocytes and plasma cells distribution within the gingival mucosa: (A) Few CD20+ lymphocytes (B-cells) present in the inflammatory infiltrate; numerous CD20- lymphocytes and plasma cells are visible; (B) Control – no CD20+ lymphocytes (B-cells) present in the lamina propria (normal histological findings); (C) Few CD79a+ lymphocytes (B-cells) present in the inflammatory infiltrate; numerous cells are negative – lymphocytes (similar proportion of CD79a-/CD79a+ lymphocytes with CD5+/CD5- lymphocytes present in Figure 5A or Figure 5C) and plasma cells; (D) Control – CD79a+ lymphocytes (B-cells) absent in the lamina propria (normal histological findings); (E) Numerous plasma cells (CD138+ cells) present in the inflammatory infiltrate; few smaller cells negative for CD138 – small T- and B-lymphocytes; (F) Control – no plasma cells are present in the lamina propria (normal histological findings). Anti-CD20 antibody immunomarking: (A and B) ×400. Anti-CD79a antibody immunomarking: (C and D) ×400. Anti-CD138 antibody immunomarking: (E and F) ×400.***

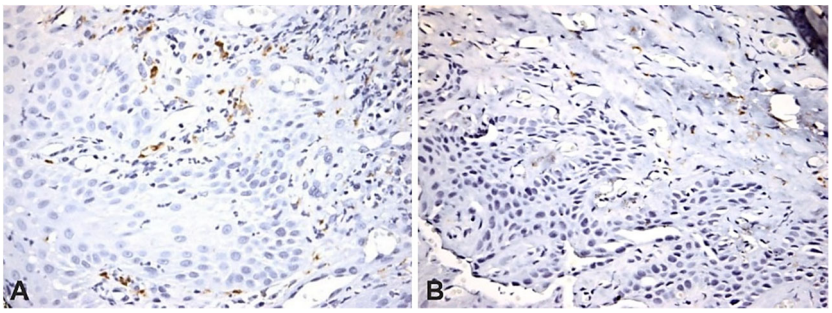

Figure 7 – ***Similar presence of histiocytes (CD68+ cells) within the lamina propria in both studied case (A) and control (B). No intraepithelial exocytosis of CD68+ cells (normal histological findings). Anti-CD68 antibody immunomarking: (A and B) ×400.***

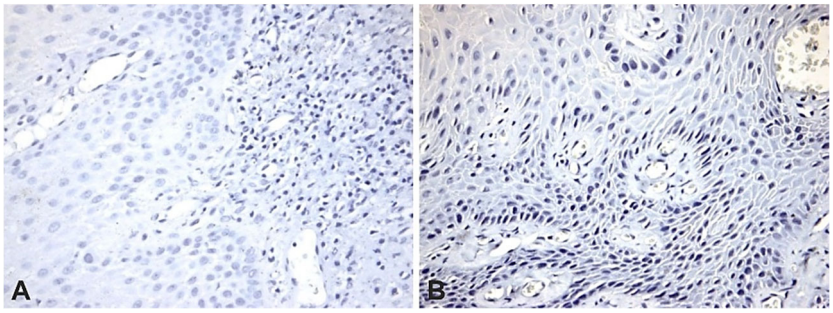

Figure 8 – ***No positivity for p53 in the epithelium in both studied case (A) and control (B) (normal histological findings in both studied case and control). Anti-p53 antibody immunomarking: (A and B) ×400.***

CCBs are drugs that are prescribed for the treatment of hypertension, angina pectoris and cardiac arrhythmias. They cause increases in gingival volume in the marginal periodontium. This undesirable side effect was first described in two case reports, in 1984 [14, 15].

The prevalence of gingival overgrowth in patients treated with CCBs is between 6.3% and 83% [16–18]. This varies depending on the patient sample, age, and the type of medication. Nifedipine is one of the CCBs that has been associated with gingival hyperplasia. The prevalence varies between 30% and 50% in Nifedipine-treated patients, compared to a prevalence of 5% in untreated controls. The percentage of patients with increased gingival volume who had been treated with Amlodipine or Diltiazem did not exceed the one in the control group [19, 20].

CCBs inhibit the L-type Ca^{2+} channel in cells and are divided into the following two categories based on their physiological effects:

- dihydropyridines, which are predominantly vasodilators and have a neutral or increased effect on vascular permeability, such as Nifedipine, Felodipine, Nicardipine, Amlodipine and Lacidipine;
- nondihydropyridines, such as Verapamil and Diltiazem, which reduce permeability and affect cardiac contractility and conduction [21].

Gingival overgrowth is prevalent in treatment with dihydropyridines and is characterized by an accumulation of ECM inside the gingival connective tissue [3]. It usually occurs within the first month of treatment.

Barak *et al.* [16] suggest an increase in doses leads to an additional increase in gingival volume; however, this has not been concurred by Akimoto *et al.* [18], James & Linden [22] or by Tam & Wanders [23].

Other side effects of the CCBs include headache, dizziness, flushing, constipation, and peripheral edema. These symptoms occur among 10–20% of patients [24, 25]. Edema is uncommon when a dihydropyridine is administered in combination with an inhibitor of the renin–angiotensin system (IRAS) [26, 27]. This is caused by a dilation of the veins by the IRAS, which helps to remove the seized fluid in the capillary bed by the dilated arterioles.

The mechanism behind gingival overgrowth remains partially unknown. There have been suggested an inflammatory or non-inflammatory mechanisms. The inflammatory theory suggests that inflammation develops because of a direct toxic effect of drugs concentrated in the crevicular gingival fluid, possibly in connection with bacterial plaque. This inflammation can lead to an increase in cytokine factors, particularly an increase of transforming growth factor-beta 1 (TGF-β1). Non-inflammatory theory points to defective collagenase activity due to increased absorption of folic acid [28], a blockage of aldosterone synthesis in the adrenal cortex, with feedback following adrenocorticotropic hormone growth and up-regulation of keratinocytes as a growth factor [29].

The present case was included in the category of complex cases, in which the systemic condition and subsequent treatment influenced the condition of the periodontal tissues, as well as the presence of the local favoring factors. Additionally, the treatment of hypertension for some patients is complex. As such, the stabilization of blood pressure to normal values may require various approaches including alternating several treatment plans, in which the patient's compliance is requisite. The present case showed that in the conditions of an antihypertensive and antilipidemic medication, a stroke occurred which necessitated a careful re-evaluation of the medication. This was however a "justification" for the patient's lesser concern about prophylactic methods for periodontal diseases, the plaque index being 100%, the previous concern for dental status being supported by the complex prosthetic treatment he had benefited from. Thus, in order not to consider from the beginning a drug side effect and to change the nature of basic antihypertensive treatment, a HP examination could clarify whether the gingival changes are inflammatory in nature or was the adverse result of CCBs. On the other hand, the statin medication that the patient taking, in addition to the primary cardioprotective effect, may had a lipid-lowering role in counteracting inflammatory phenomena. Studies have

shown that the locally and/or systemically administration of statins had beneficial effects on periodontal tissue, such as enable antioxidants, generate anti-inflammatory effects by decreasing the level of proinflammatory interleukin (IL)-1 and increasing the level of IL-10 cytokine, stimulate angiogenesis, improve endothelial function, and bone regeneration [30, 31].

Gingival changes may occur as side effect of several drugs, most common culprits being anticonvulsant agents, CCBs and Cyclosporin A. In this case was important to look for the specific morphological lesions present in the biopsy. There had had to be considered that the morphological substrate of gingival lesions consisted in a general increase of extracellular volume of periodontal tissue (collagen fibers and matrix) and less proliferation of cells; technically, due to these alterations, the most appropriate term to use for drug-related gingival enlargement is "gingival overgrowth" and not "gingival hyperplasia" since it does not involve a cellular proliferation [32].

In fact, the main HP alterations are linked to the *lamina propria*, the epithelial lesions being secondary to those of the connective tissue [33]. There is some fibroblast proliferation or, at least, fibroblastic hyperfunction, with production of glycosaminoglycans (ECM) and collagen fibers [34]; the fibroblasts activation is more likely determined by the inhibition of Na^+ and Ca^{2+} ions influx; the cation influx alteration determines a diminished folic acid intracellular absorption, with subsequent alterations of matrix metalloproteinases (MMPs) [35]. The local lack of activated collagenases favors the collagen deposition. In the incipient phases, the collagen is immature (collagen IV), lately thick, maybe hyalinized bundles of collagen fibers are deposited between the rete ridges [33]. Downregulation of MMP8 and MMP11 was identified in gingival overgrowth due to immunosuppressive drugs, such as Cyclosporin A and Mycophenolate mofetil [36]; decreased expression of MMP1 and MMP3 was reported in gingival fibroblasts exposed to Cyclosporin A [37]. The most prominent alterations are the accumulation of the inflammatory cells within the *lamina propria*, with significant proportion of plasma cells.

In this case, the HP exam showed a significant increase of cellular component in *lamina propria* due to a prominent chronic inflammatory infiltrate consisting of numerous T- and much fewer B-lymphocytes, numerous plasma cells and few histiocytes. No neutrophils or eosinophils were present within the inflammatory infiltrate. Thereby, the severity of the inflammatory process could be linked to the plaque development and to the xerostomia, which may occur as drugs side effect.

Thus, in this case, the gingival enlargement wasn't the side effect of the Amlodipine, the change of medications wasn't mandatory, and the periodontal treatment had to be focused on resolution of an inflammatory process due to the local factors for plaque accumulation.

Conclusions

In cases where periodontal pathological changes are the result of the presence of several local and systemic factors, detailed complementary examinations are required, which, even if they involve additional costs, may clarify the nature of HP changes and the management of periodontal treatment. Systemic medication may influence the clinical features and the HP changes may suggest the influence of inflammation in the periodontal manifestation by increasing volume. Further studies, relevant case studies, are needed to gain knowledge on this issue.

Conflict of interests

The authors declare that they have no conflict of interests.

Author contribution

Sabina Andrada Zurac has equal contribution to this paper as the first author.

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