Amlodipine-induced gingival overgrowth – Review and Case Report

Crescimento gengival induzido por Amlodipina - Revisão e Relato de Caso

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ABSTRACT

Gingival overgrowth or enlargement is among one of the most important clinical features of gingival pathology frequently seen in periodontal clinic. Gingival overgrowth is a serious side effect that accompanies the use of amlodipine. Amlodipine is a comparatively new calcium channel blocker and is being used with increasing frequency in the management of hypertension and angina pectoris. Pertinent management depends on precisely diagnosing the origin of overgrowth. Cessation or change of drug and meticulous plaque control often leads to regression of the lesion, which however might need surgical correction for optimal maintenance of gingival health. The purpose of this article is to present a case report and highlight significant aspects of Amlodipine-Induced Gingival Overgrowth (AIGO).

Keywords: Amlodipine, Gingival overgrowth, Periodontics.

RESUMO
O crescimento ou aumento gengival está entre uma das características clínicas mais importantes da patologia gengival, freqüentemente observada na clínica periodontal. O crescimento gengival é um efeito colateral sério que acompanha o uso de amlodipina. A amlodipina é um bloqueador dos canais de cálcio comparativamente novo e está sendo usado com frequência crescente no tratamento da hipertensão e da angina de peito. O manejo pertinente depende do diagnóstico preciso da origem do crescimento excessivo. A cessação ou troca da droga e o controle meticuloso da placa, freqüentemente levam à regressão da lesão, que, entretanto, pode necessitar de correção cirúrgica para a manutenção ideal da saúde gengival. O objetivo deste artigo é apresentar um relato de caso e destacar aspectos significativos do crescimento gengival induzido por Amlodipina (CGIA).

Palavras-Chave: Amlodipina, Crescimento gengival, Periodontia.

1 INTRODUCTION

Drug-induced gingival overgrowth was first reported in 1939 by Kimball, with chronic usage of the antiepileptic drug phenytoin (Kimball, 1939). The first report regarding gingival overgrowth by the administration of amlodipine was published in 1994 (Seymour, Ellis, Thomason, 1994). Currently, more than 20 prescription medications are associated with gingival hyperplasia (Gittaboyina et al. 2016). Drug-induced gingival overgrowth is a common consequence of the administration of some anticonvulsants, immunosuppressants and Calcium Channel Blockers (CCBs) (Joshi & Bansal 2013). Recently amlodipine has been used in cases of patients infected by SARS-Cov-2. Zhang et al. (2020) demonstrates that calcium channel blocker *amlodipine besylate* therapy is associated with reduced case fatality rate of Covid 19 patients with hypertension.

According to Goldfraind, in 2017, calcium channel blocking agents are generally classified into three groups according to their chemical structure: benzothiazepines (diltiazem); phenylalkylamines (verapamil); and the dihydropyridines (amlodipine, nifedipine and nisoldipine). All these agents inhibit the movement of calcium ions across the cell membrane by blocking the L-type calcium ion channel (which are the predominant calcium channels in the myocardium and vascular smooth muscles). The main result is a coronary artery dilatation. Gittaboyina et al. (2016) affirm that CCBs are considered as one of the etiologic factors among patients seeking dental care for drug-induced gingival enlargement or overgrowth.

Livingstone & Livingstone (2012) describes that the dihydropyridine calcium channel blockers a group that includes amlodipine, are a common choice for treatment of hypertension, cardiac arrhythmias and chest pain related to angina pectoris. Amlodipine, which is both low cost and taken once daily, is the one of the most prescribed agents (Tung et al. 2015). Amlodipine has an inherently long pharmacokinetic half-life (more than 24 hours), whereas, in contrast, nifedipine has an inherently short half-life (Toal, Merdeith & Elliot 2012)

In the past the prevalence of Amlodipine-Induced Gingival Overgrowth (AIGO) was 1.7% to 3.3% (Tejnani et al. 2014). Lately, the data suggests that there has been an increase in the number of these cases. Amlodipine is the most preferred drug for long term maintenance of hypertensive and angina patients, it is worth understanding the various variables related to one of its major side effects, the gingival overgrowth (Morikawa et al. 2021). Gaur & Agnihotri (2018) affirms that the pooled data in the present review revealed increased rate of gingival overgrowth (26.7%) among subjects on amlodipine. John et al. (2020) wrote that gingival hyperplasia is a rare side effect of this drug. Patients undergoing monotherapy with amlodipine had less gingival overgrowth than those taking nifedipine (Chang, Yang & Lai 2012).

The importance of dental plaque as a cofactor in the etiology of drug-associated gingival overgrowth has been recognized in the most recent classification system for periodontal diseases. In this classification, “drug-induced gingival enlargements” are categorized as “plaque-induced gingival diseases modified by medications” (Dongari-Baqtzoglou 2004, Bharti & Bansal 2013). Kataoka et al. (2005) pointed out that the pathology of drug-induced gingival overgrowth is not definitively known, these disorders seem to be induced through disruption of homeostasis of collagen synthesis and degradation of gingival connective tissues. Lafzi, Farahani & Shoja (2006) describes acanthosis of epithelial lining, elongation of rete ridges, and sparse fibroblasts in a dense collagenous matrix are the underlying histological changes.

The presence of amlodipine in the gingival fluid can be important to determine the etiology of gingival overgrowth. Moreover, according to Seymour, Ellis & Thomason (1994), the significance of this finding in relation to the pathogenesis of this unwanted effect remains to be elucidated. Ellis et al. (1992) measured the pharmacokinetics of nifedipine in plasma and gingival crevicular fluid (GCF) of nine patients receiving this drug for angina and hypertension. The two patients with low (undetectable) GCF nifedipine did not have overgrowth. The authors purpose that gingival tissues sequester

nifedipine and that the extremely high nifedipine concentrations predispose the tissues to overgrowth. Seymour, Ellis & Thomason (1994) reported three cases of amlodipine induced gingival overgrowth and demonstrates a sequestration of amlodipine in the gingival crevicular fluid. Like nifedipine, amlodipine sequestration into GCF appears to be linked with gingival overgrowth.

Lauritano et al. (2019) suggest that these results seem to indicate a possible role of amlodipine in the inflammatory response of human gingival fibroblasts exposed to drugs. Joshi & Bansal (2013) wrote that a synergistic enhancement of collagenous protein synthesis by human gingival fibroblasts is found when these cells are exposed simultaneously to calcium channel blockers and elevated levels of interleukin-1β (a proinflammatory cytokine) in inflamed gingival tissues.

Two mechanisms have been suggested (non-inflammatory and inflammatory) for the pathology of gingival overgrowth. The proposed non-inflammatory mechanisms include defective collagenase activity due to decreased uptake of folic acid, increase in ACTH level, and upregulation of keratinocyte growth factor (KGF). Alternatively, inflammation may develop because of direct toxic effects of concentrated drug in crevicular gingival fluid (CGF) and/or bacterial plaques. This inflammation could lead to the upregulation of several cytokine factors such as TGF-ß1 (Lafzi, Farahani & Shoja 2006, Srivastava et al. 2010).

Triveni, Rudrakshi & Mehta (2009) affirms that clinical manifestations of gingival overgrowth frequently appear within one to three months, after initiation of treatment with the associated medications. Gingival overgrowth normally begins at the interdental papillae, is more frequently found in the anterior segment of the labial surfaces, and due to the concomitant unesthetic appearance and the formation of new niches for the periopathogenic bacteria is considered a serious adverse drug reaction (Lafzi et al. 2006, Samudrala et al. 2016).

Chang, Yang & Lai (2012) affirm that treating the gingival overgrowth lesion itself can be complicated due to the inflammation superimposed on fibrotic tissue enlargement. Several investigations indicated that the severity of gingival overgrowth is related to the level of oral hygiene and gingival inflammation. Triveni et al. (2009) report a case of Amlodipine-Induced Gingival Overgrowth (AIGO) that was treated in the following phases: (1) thorough Phase-1 therapy (nonsurgical treatment), (2) substitution of the drug, (3) surgical excision of the residual gingival overgrowth and (4) maintenance and supportive therapy. Mavrogiannis et al. (2006) wrote that surgical treatment is often

the most reliable option and scalpel gingivectomy remains the treatment of choice. Morikawa et al. (2021) recommends periodontal surgery specially gingivectomy on the sites of hard fibrous swelling.

2 CASE REPORT

Adult patient, I.R.S., 48 years old, went to the dental clinic of the State University of Ponta Grossa (UEPG) with the main complaint of gingival bleeding. In the anamnesis, the patient reported having arterial hypertension and to control the disease, he has been using two medications for more than five years: amlodipine 10mg (as *amlodipine besylate*) and Losartan 50mg.

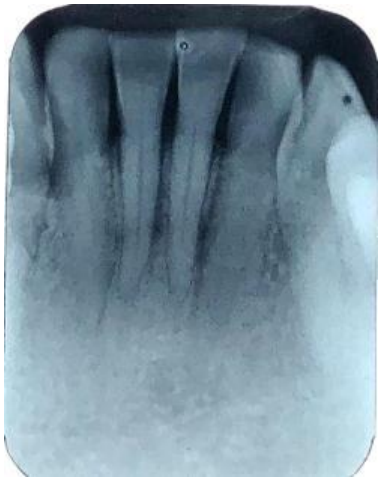
Intraoral examination revealed gingival overgrowth in most sites of the gingiva (especially at the interdental papilla and marginal gingiva), covering almost one-third of the lower anterior teeth (Figure 1). Typically, it is not seen in edentulous areas and gingiva present a fibrotic consistency.

Figure 1. Gingival overgrowth especially at the interdental papilla and marginal gingiva, covering almost one-third of the lower anterior teeth. In superposition to periodontitis, a gingival overgrowth was observed.

The measurement of periodontal probing depth (PD) and clinical attachment loss (CAL) were passed on to software that generated a complete *periogram*. Bleeding on probing (BOP) was observed in the inferior anterior sites and represent clinical sign as indicator of the periodontal condition and disease progression. The clinical probing depth has reached up to 6 to 8 mm in some sites. The areas with gingival

overgrowth, however, were painless and did not spontaneously bleed. The periapical radiographic examination showed an evident clinical attachment loss (alveolar bone loss) in the inferior anterior area (Figure 2).

Figure 2. The periapical radiographic examination showed an evident clinical attachment loss (bone resorption) in the inferior anterior area. Small bone craters are observed.



The periodontal diagnosis demonstrated the presence of a generalized (moderate) chronic periodontitis. In the inferior anterior area, in superposition to periodontitis, a gingival overgrowth was observed.

Treatment was started with basic procedures (non-surgical periodontal treatment) that include guidance on oral hygiene, use of daily mouthwashes of 0.12% chlorhexidine and scaling and root planning. After 21 days of instrumentation, the patient was returned and assessment of the situation regarding gingival overgrowth. It was found that the regression of gingival overgrowth was exceedingly small and so it was decided to perform surgical periodontal treatment. The first surgical option was gingivectomy, however, considering the extensive clinical attachment loss of the inferior anterior sites, the planning was changed to a Modified Widman Flap Procedure (Figure 3). Repositioning the flap and suturing phase is showed in Figure 4.

Figure 3. The flap is displaced showing bone resorption and interdental osseous craters. Gingivectomy could not access these bone defects.

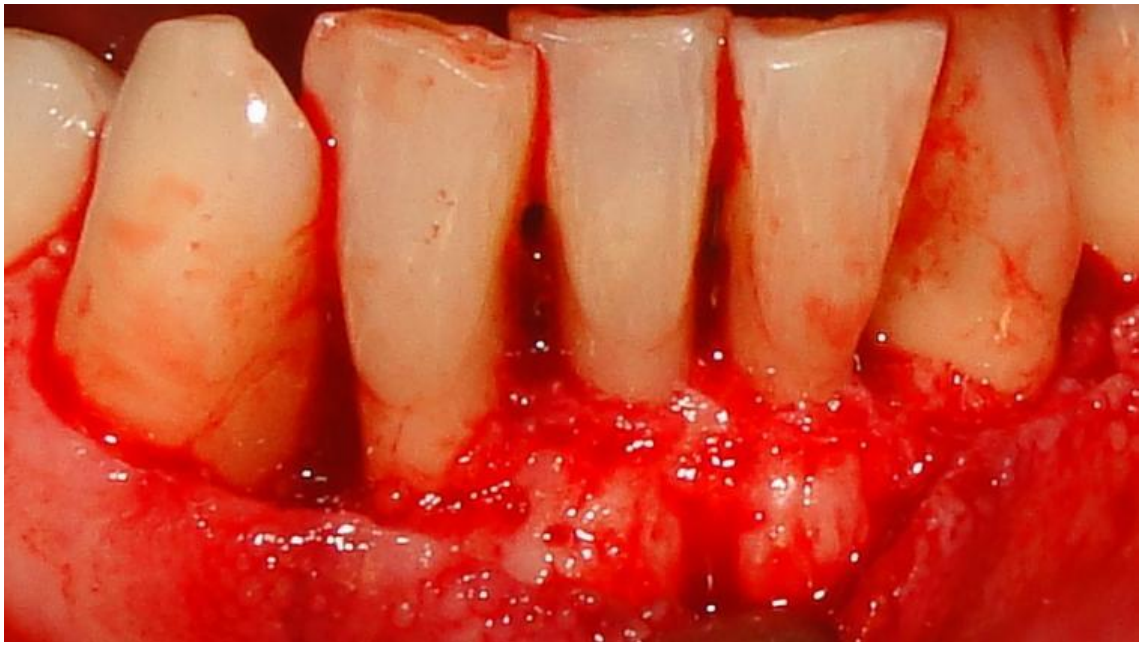
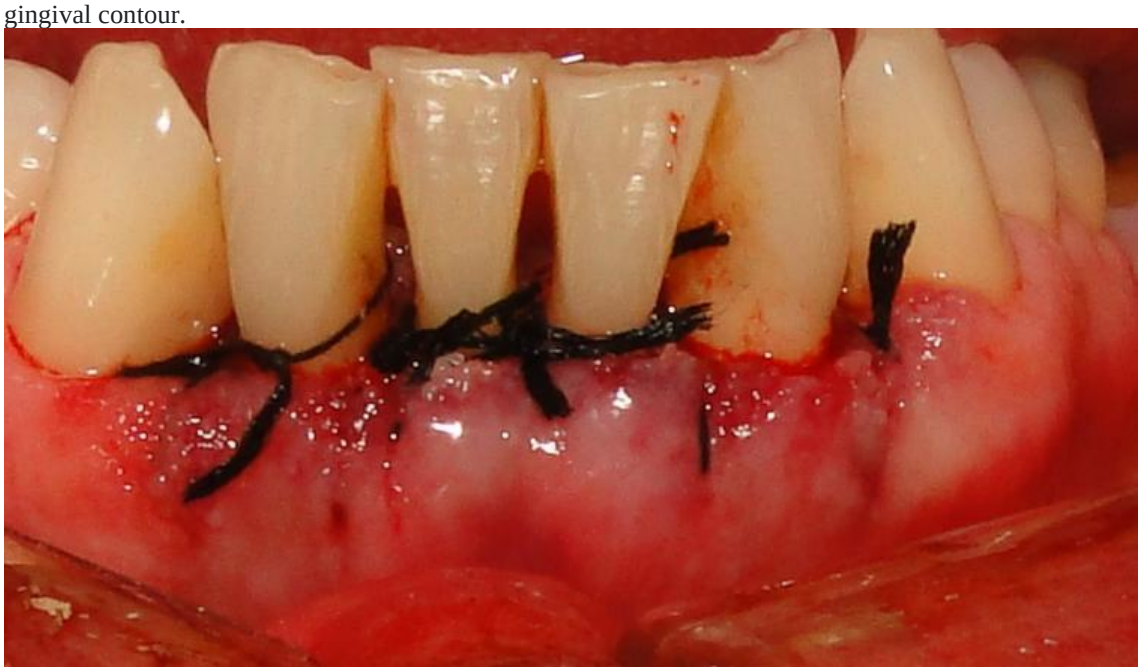


Figure 4. Repositioning the flap and suturing phase. In some sites, gingivoplasty was used to improve the gingival contour.



The clinical result after 15 days was excellent from the aesthetic point of view, to eliminate niches for the periopathogenic bacteria and to facilitate oral hygiene (Figure 5).

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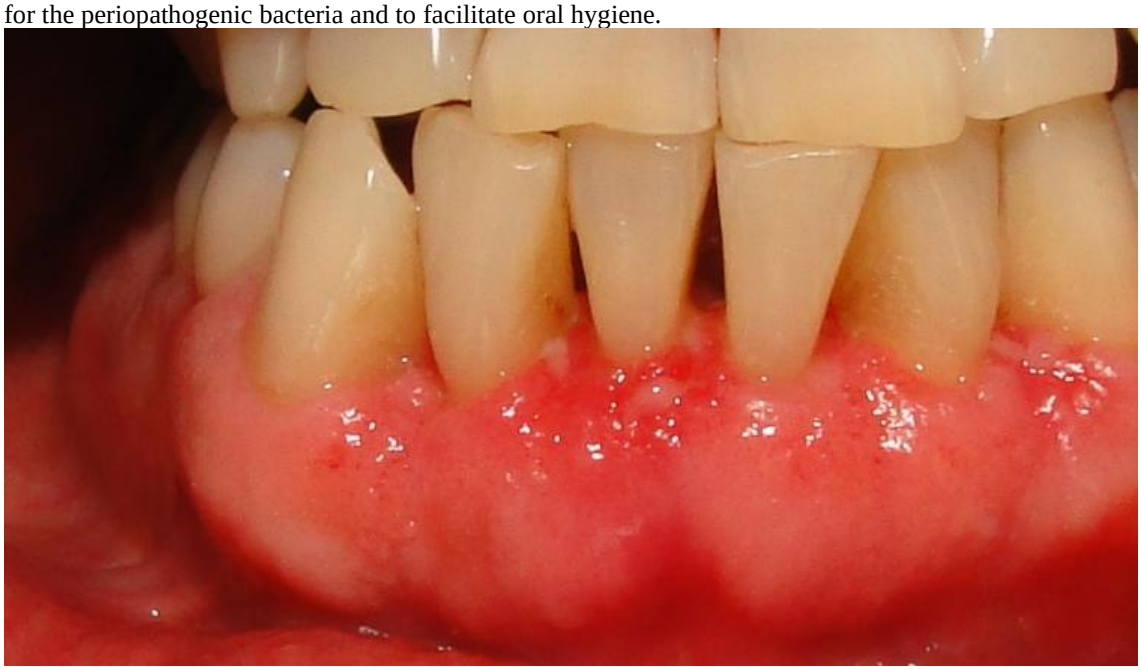


Postoperative clinical aspect after 18 months shows the lower anterior region of both arches, upper and lower, the elimination of both periodontal pockets and gingival overgrowth and the maintenance of satisfactory aesthetics (Figure 6).

Figure 6. Postoperative clinical aspect after 18 months. The clinical case remains stable, both in the upper and lower arch, without periodontal pockets and with satisfactory aesthetics. However, the fibrotic consistency remains.

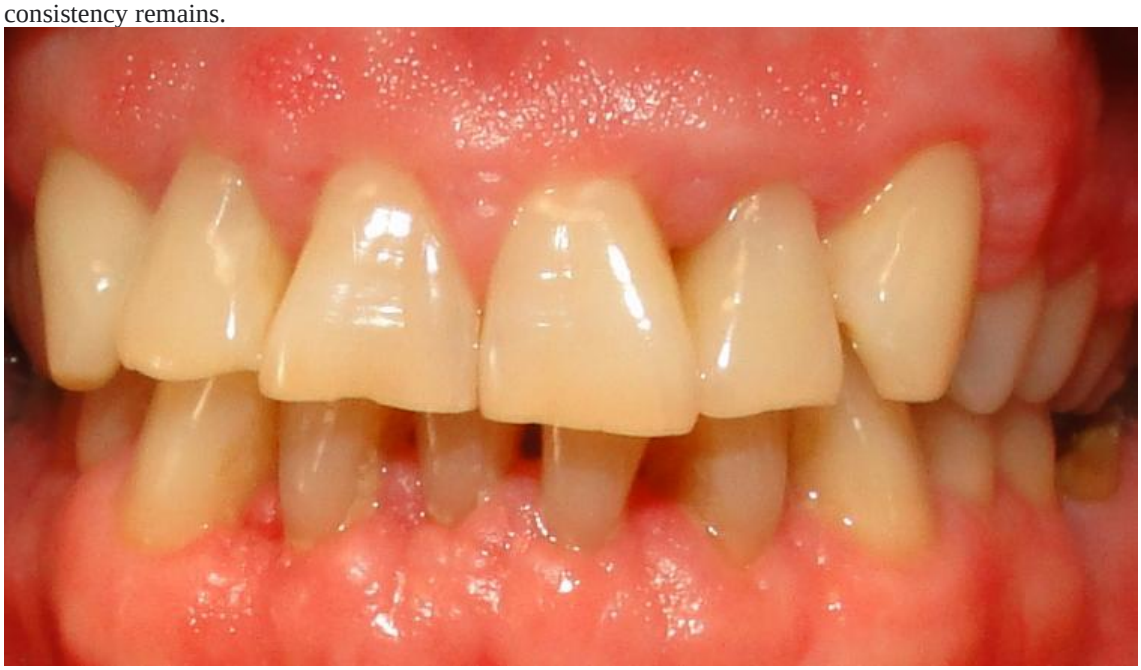
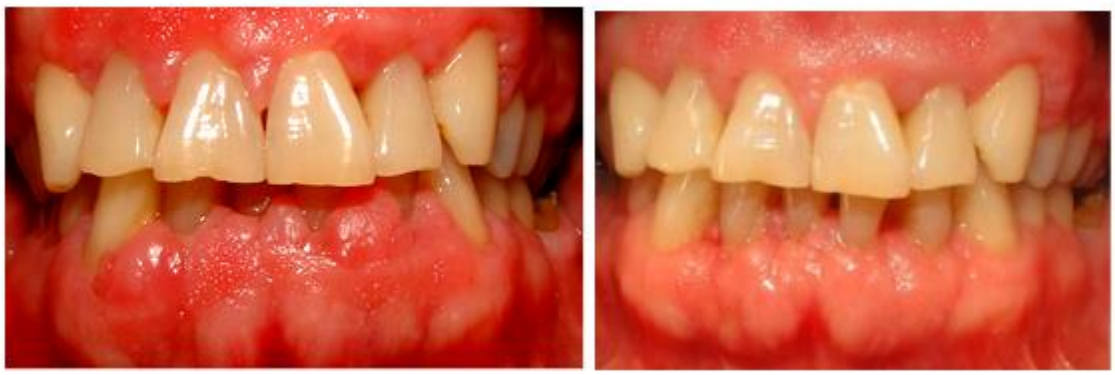


Figure 7 shows the initial and final case after periodontal and surgical treatment.



A B

Figure 7. In A the initial clinical case is observed. Alterations in the papillae of the upper arch and gingival overgrowth in the lower arch. In B shows the elimination of the periodontal pockets and the papillae of the upper arch are normal. In the lower anterior region, the elimination of the gingival overgrowth and satisfactory esthetics are observed.

3 DISCUSSION

Seymour et al. (1996) presented a multifactorial model for the pathogenesis of drug-induced gingival overgrowth. There would be an interaction of several factors, which expand in the interaction between the drug and the metabolite with the gingival fibroblasts. Predisposing factors for these changes are age, genetic predisposition, pharmacokinetic variables, drug-induced alterations in gingival connective tissue homeostasis, histopathology, ultrastructural factors and inflammatory changes, and drug-induced action on growth factors.

Several authors pointed out that one of the initial forms of treatment is to replace the medication. Tripathi et al. (2015) wrote that treatment consists of substitution of drugs, if possible, with patient's physician consent, in substitution of amlodipine with isradipine, lercanidipine and lacidipine, which are the newer fourth-generation dihydropyridines. Gittaboyina et al. (2016) related that in a patient the amlodipine 5 mg/day was replaced with atenolol 50 mg/day twice daily by the physician. There are cases where the physician indicates two antihypertensive drugs. Tung et al. (2015) revealed a clinical report where patients was treated with a Fixed-Dose Combination of Amlodipine/Valsartan. Drug induced Gingival Overgrowth can be treated initially with drug substitution followed by advocating diligent plaque control measures (nonsurgical treatment). In our clinical report, the patient has been using two medications for more than five years: Amlodipine 10mg and Losartan 50mg (that is an angiotensin II receptor antagonist and that does not cause gingival overgrowth). Due to the severity of the patient's hypertension, we have not changed the medication prescribed by the doctor. Our

therapy followed the treatment protocol presented by Triveni et al. (2009). Gittaboyina et al. (2016) wrote that the treatment aspect included scaling and root planning, substitution of the drug, the surgical excision, and the maintenance and supportive therapy resulting in an excellent clinical outcome.

According to Mavrogiannis et al. (2006) non-surgical techniques can limit the occurrence of this unwanted affect (gingival overgrowth), reduce the extent of plaque-induced gingival inflammation, and reduce the rate of recurrence. Wherever possible this management strategy should be adopted first. Surgical treatment is often the most reliable option and scalpel gingivectomy remains the treatment of choice (Goldman 1951).

In this clinical case report, we have opted by Modified Widman Flap surgery (Ramfjord & Nissle 1974) at the mandibular incisors due to the severity probing depth (around 6-8 mm) and where false periodontal pockets (or pseudo pocket due to gingival overgrowth) and true periodontal pockets (apical migration of junctional epithelium, connective tissue and loss of clinical attachment) are associated. After 15 days, the clinical result was excellent from the aesthetic point of view, to eliminate niches for the periopathogenic bacteria and to facilitate oral hygiene. One of the possible forms of tissue repair may include the presence of fibrosis or *fibrotic* wound healing (Figure 6 and 7, B). Is a form of wound healing in which connective tissue can replaces normal parenchymal tissue. Fibrosis is characterized by excessive accumulation of collagen and other extracellular matrix (ECM) components. However, fibrosis can proceed without evidence of an inflammatory component (Wynn 2008).

According to Castelino, Buch & Laxmana (2021), surgical approach becomes necessary to remove excess tissue, regain appearance and function, as well as to eliminate any pockets (as we have achieved with the Modified Widman Flap); the basic surgical method involves gingivectomy and gingivoplasty. The recurrence of gingival overgrowth can occur irrespective of the treatment provided if the offending drug is not stopped or replaced with another class of drug. Nasu, Miyashita & Nakagawa (2021) wrote that significant improvement in gingival overgrowth can occur with basic periodontal treatment, surgery and sustained intensive follow-up without adjusting calcium channel blockers.

4 CONCLUSION

Non-surgical periodontal treatment and Modified Widman Flap Procedure were effective for the elimination of the gingival overgrowth and satisfactory esthetics are observed after 18 months follow-up.

Further investigations are required to develop appropriate management strategies to prevent recurrence of gingival overgrowth.

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