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Local Drug Delivery- A Tactical Entreaty Enhancing the Periodontal Repair: A Case Report

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ABSTRACT

Gingival overgrowth is an undesirable side effect, associated with some classes of drugs. Various predisposing factors and etiologic agents like age, drug doses, genetic factors, plaque induced inflammation etc. have been proposed in the etiopathogenesis of the disease. Treatment of such condition when it interferes with aesthetics, function and occlusion includes non-surgical and surgical approach. However, the efficacy of mechanical debridement of plaque biofilm is limited due to the inaccessibility to the periodontal pathogens in deeper pockets. Chemotherapeutic agents have been widely used as adjuncts to conventional non-surgical approach for treating various forms of periodontal diseases. But due to the side effects associated with the systemic route, local delivery of antimicrobial agents to the target site has been advocated. This case report highlights the role of local drug delivery in conjunction with scaling and root planing for the management of drug induced gingival enlargement.

KEYWORDS

Gingival overgrowth; Non-surgical; Chemotherapeutic agents; Local drug delivery

INTRODUCTION

The gingiva and associated periodontal soft tissues might show enlargement in response to numerous interactions between the host and the environment [1]. Gingival enlargements can manifest as an increase in the mass and volume of gingival tissues ranging from mild to severe enlargement of papillary or marginal gingiva. The condition shows greater predilection for the anterior than the posterior teeth and the buccal gingivae than the lingual/palatal gingivae [2].

Though such enlargements are usually an inflammatory response to bacterial plaque biofilm**,** however**,** increased susceptibility as a result of systemic factors or conditions should always be kept into consideration during the course of patient evaluation and treatment planning [1]. Therefore**,** based on etiopathogenesis, enlargements can be categorized as inflammatory, drug induced, those associated with systemic conditions or diseases, neoplastic or false enlargements [3].

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Drug-induced gingival overgrowth or enlargement occurs as a side effect of the administration of drugs intended mainly for non-dental treatments [4]. Drugs causing gingival enlargement are broadly classified into three categories: anticonvulsants, calcium channel blockers, and immunosuppressants. Although the pharmacological effects of each of these classes of drugs are different and directed towards varied number of primary target tissues, all of them seem to behave quite similarly on a secondary target, i.e., the gingival connective tissue, thereby resulting in common clinical and histopathological findings [5]. Besides, there are numerous factors that influence the relationship between the drugs and gingival tissues namely; age, genetic predisposition, presence of preexisting plaque, and gingival inflammation [4].

Calcium channel blockers (CCBs), a category of drugs especially developed for the management of angina pectoris, hypertension, supraventricular arrhythmias and some forms of acute myocardial infarction have different chemical structural orientation and mechanism of actions [6] i.e they act by interfering with the mobilization of calcium intracellularly by blocking the influx of calcium ions across the cell membranes of cardiac and smooth muscle cells [1]. Gingival overgrowth as a consequence of calcium channel blockers (Nifedipine, Amlodipine, Verapamil) has been widely reported in literature [2]. The mechanism of pathogenesis of CCB induced gingival enlargement is considered to be a multifactorial model involving an interaction between drug and metabolite with the gingival fibroblasts [7]. It has been hypothesized that only a subset of patients treated with these drugs show signs of enlargement due to the presence of fibroblast population with an abnormal susceptibility to the drug. Additionally, it has been proposed that the existence of different proportions of fibroblastic subsets exhibit a fibrogenic response to these drugs [5].

The preliminary management of a case of drug induced enlargement should be directed towards substitution/ withdrawal of the offending drug in consultation with the physician, followed by non-surgical periodontal therapy and oral hygiene reinforcement. Non-surgical approaches primarily intend to reduce the inflammatory burden in the gingival tissues, thereby delaying or avoiding the need for surgical intervention [4]. Scaling and root planing is a gold standard non-surgical treatment modality for periodontal diseases which removes the subgingival biofilm and calculus mechanically. However, these procedures have some limitations such as inability to reach the deep pockets and furcation areas thereby, failing to reduce or eliminate the anaerobic pathogens at the base of the pocket [8], [9]. Hence, Goodson et al in the year 1979 proposed the concept of Local Drug Delivery in order to complement the non-surgical approach thereby, allowing the use of antimicrobials that can be locally delivered into the inflamed gingival tissues such as metronidazole, chlorhexidine, tetracycline, doxycycline and minocycline [10].

Therefore, the present case report highlights the role of local drug delivery as an adjunct to scaling and root planing in the management of a case of drug induced gingival enlargement.

CASE REPORT

A 38-year-old female patient reported to the Department of Periodontology, Sri Guru Ram Das Institute of Dental Sciences and Research, Amritsar with the chief complaint of swelling of gums in the lower front region and pain in lower right back region of jaws since 5-6 months. Patient also complained of pus discharge and bleeding while brushing from all the teeth.

Past medical and dental history

Patient was hypertensive and on medication (Calcium channel blockers) for the same for past 3 years. However, there was no relevant past dental and drug history.

Intra oral examination

Revealed generalized gingival inflammation with bleeding on probing. Localized gingival enlargement w.r.t mandibular anterior teeth, generalized pocket formation, generalized attrition, abscess formation w.r.t. 46, 47 and moderate stains & calculus (Figure 1 and Figure 2).

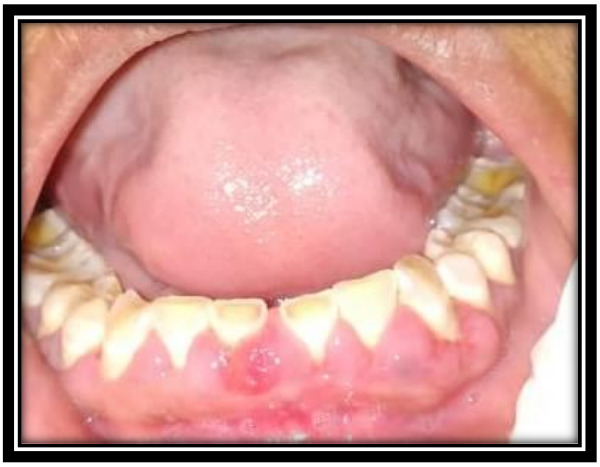

Figure 1: Localized Gingival enlargement in mandibular anteriors.

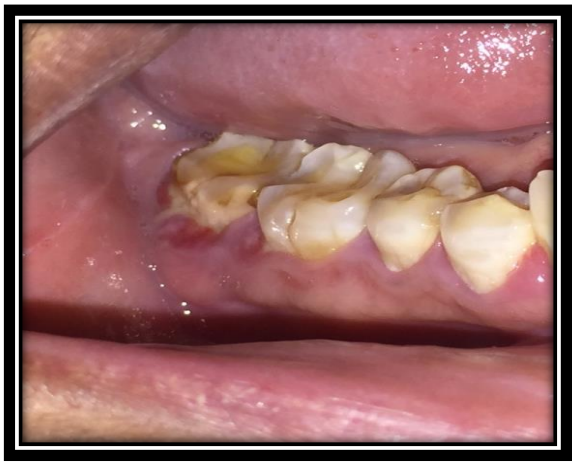

Figure 2: Abscess formation in the region of 46, 47.

Extra oral examination

Did not reveal any swelling or asymmetry of the face. TMJ was normal and there was no pain, clicking sound on opening / closing the mouth. Lymph nodes were also non palpable.

Radiographic examination

Orthopantomogram (OPG) showed moderate horizontal bone loss and furcation involvement w.r.t 47 (Figure 3).

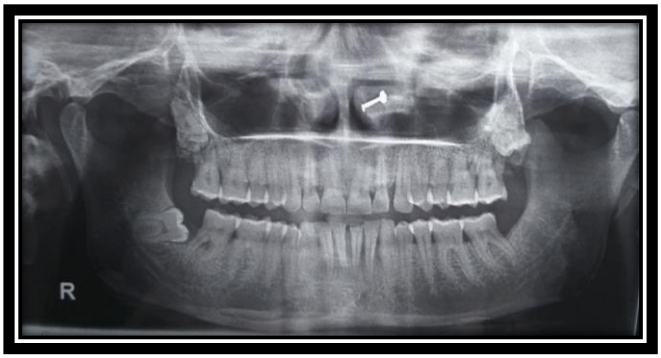

Figure 3: Orthopantomogram showing moderate horizontal bone loss and furcation involvement w.r.t 47.

Diagnosis and treatment

On the basis of clinical and radiological findings, a provisional diagnosis of Drug induced gingival enlargement was made. The patient was first sent to the physician for drug substitution and was put on chemical plaque control regime. After physician consultation (substitution of calcium channel blockers with beta blockers) and consent, the treatment plan was formulated and an informed written consent was signed by the patient.

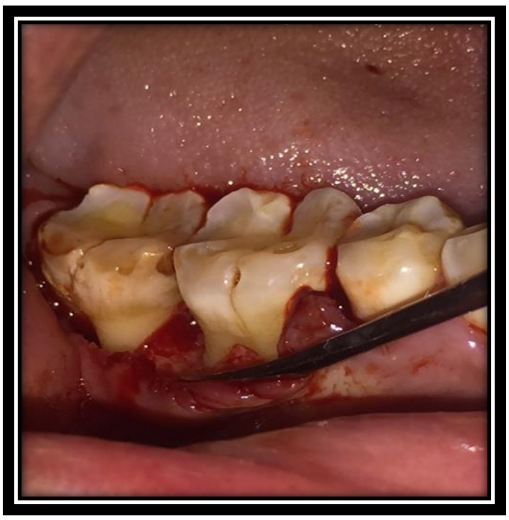

Figure 4: Abscess drainage by open flap debridement.

Before periodontal therapy, patient was sent for hematological investigations (Hb, TLC, DLC, BT, CT, HIV, HBV, HCV) to rule out any other underlying cause. After all the tests appeared within normal limits, Phase I therapy (scaling and root planing) was carried out with ultrasonic scalers and Gracey curettes. Patient was put on maintenance therapy which included brushing twice daily,

rinsing with 0.2% chlorhexidine mouth rinses and was asked to report after 7 days.

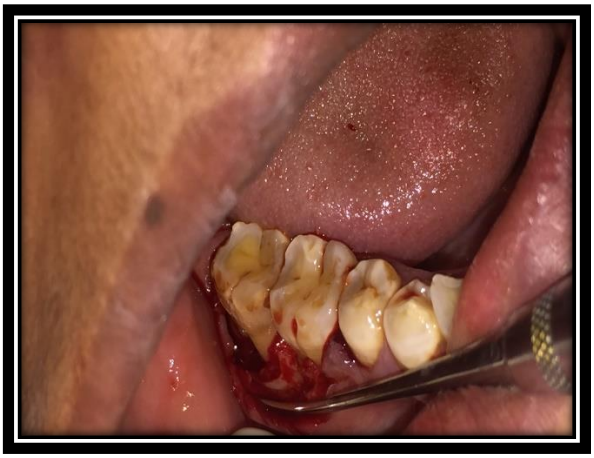

Figure 5: Abscess drainage by open flap debridement.

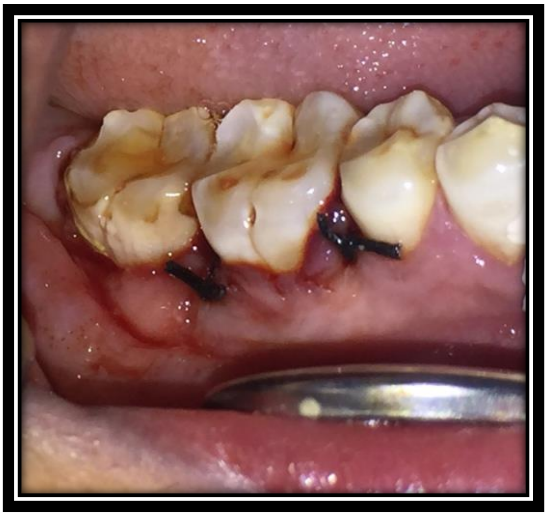

Figure 6: Wound closure by 5-0 silk suture.

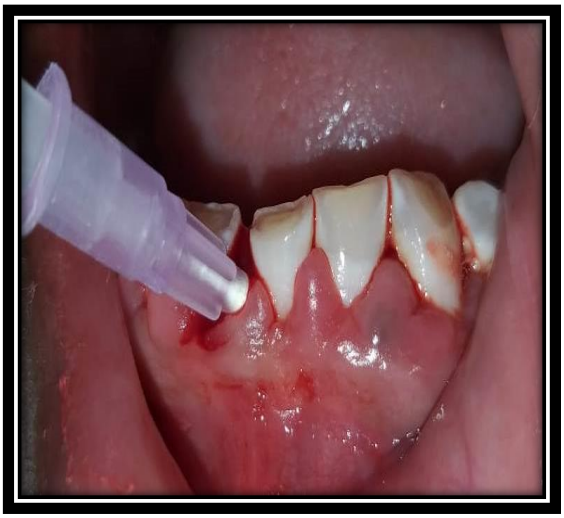

Figure 7: Local drug delivery with Metrohex gel.

On the recall visit, there was slight improvement in the gingival condition and the abscess in the area of 47 persisted. Hence, abscess drainage by means of open flap debridement under local Anaesthesia (1: 2,00,000 Adrenaline) was performed in the molar region and the wound was closed by means of 3-0 silk suture (Figure 4, Figure 5 and Figure 6). In addition to this, Local drug delivery with a combination of chlorhexidine and Metronidazole gel (METROHEX GEL) was performed in the mandibular anteriors. The gel was dispensed directly into the inflamed gingival tissues after thorough curettage by means of syringe (Figure 7). Patient was prescribed antibiotics and anti-inflammatory drugs and oral hygiene instructions were reinforced.

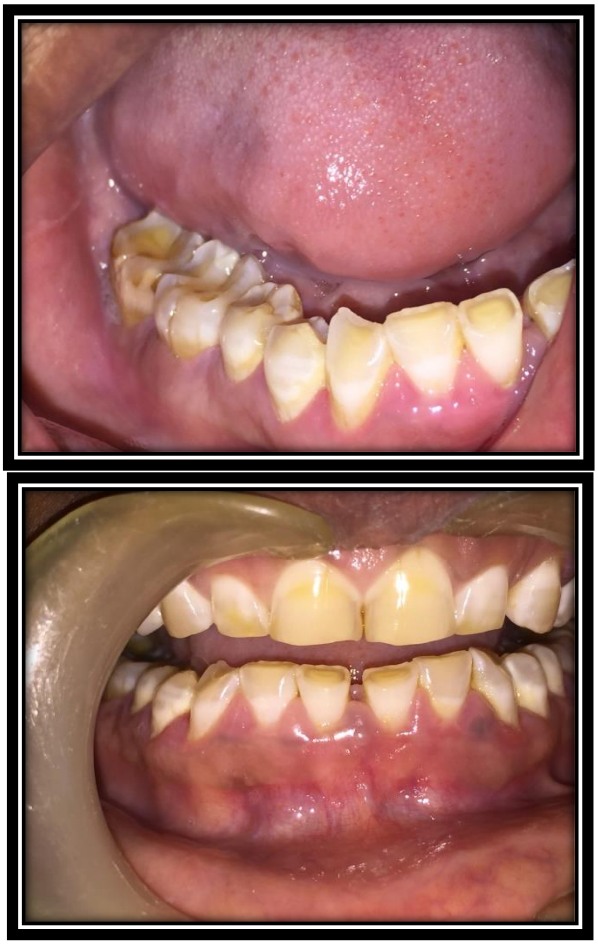

Figure 8 and Figure 9: Post-operative views after 1 week.

After 1 week, sutures were removed and the patient showed considerable improvement in gingival health and there was complete resolution of gingival inflammation (Figure 8 and Figure 9). The patient did not complain of

bleeding or pus discharge and the gingiva also showed normal colour and texture. Patient was put on a 1 and 3 months recall visit (Figure 10 and Figure 11) in order to evaluate the gingival condition.

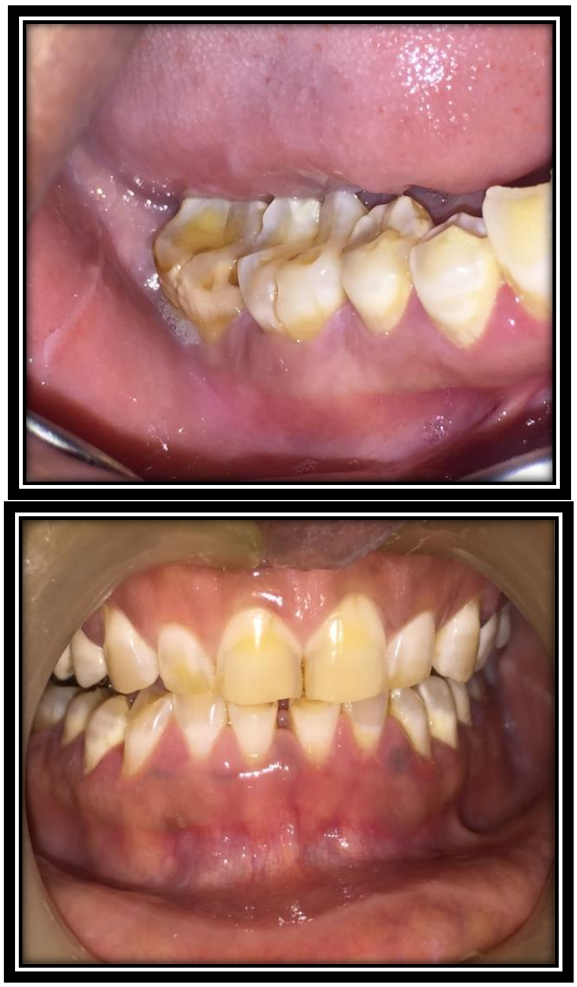

Figure 10 and Figure 11: Post-operative views after 1 month.

DISCUSSION

Traditional periodontal therapeutic modalities aimed to alter the periodontal environment to the one that is less conducive to bacterial plaque retention in the close vicinity of gingival and periodontal tissues [11]. The mechanical therapy primarily intends to eradicate gingival inflammation, eliminate bleeding, reduce periodontal pocket depth, arrest destruction of soft tissues, and bone [12]. However, with the increasing knowledge of the bacterial etiology of periodontal diseases, and in particularly the specific plaque hypothesis, a more direct approach, using antibacterial agents has become an integral part of the treatment regimen [11]. These chemotherapeutic agents can be administered systemically or locally.

The oral route of antibiotic administration, however, has many systemic side effects namely inadequate drug concentration reaching the pocket, the concentration rapidly falling to subtherapeutic levels, need for frequent dosing, patient incompliance, toxicity and development of tolerance and microbial resistance. Since the disease is confined to the periodontal tissues, thus, local delivery of the antimicrobial agent directly in the pocket itself seems to be the most suitable option [9]. It has been observed that the locally delivered drugs can attain 100-fold higher concentrations of an antimicrobial agent in subgingival sites in comparison to the systemic drug regimen. This in turn reduces the total patient dose by over 400-fold, thereby reducing the potential adverse effects associated with the use of systemic antibiotic drug regimens and development of drug-resistant microbial populations at non oral body sites [13].

Local delivery of antimicrobials in periodontal pockets can be done with fibers, films, microparticles and gels made of biodegradable or non-biodegradable polymers [14]. The choice of these antimicrobial agents for treatment of periodontal diseases must be based on the nature and bacterial etiology of the infection [15]. A variety of antimicrobial agents have been investigated for their role as local drug delivery agents in conjunction with non-surgical periodontal treatment modality. These include tetracyclines, doxycycline, minocycline, chlorhexidine and metronidazole.

In the present case, the primary aim of non-surgical approach was to decrease the inflammatory burden in the gingival connective tissue and ultimately eliminate the need for surgery. Conservative management by means of drug substitution, mechanical debridement, home care

prophylactic measures helped in reducing the pathogenic load. Reduction in gingival enlargement has been observed in cases where calcium channel blockers are substituted by a structurally different class of antihypertensive drugs such as the angiotensin-converting enzyme inhibitor (enalapril), Beta-blockers (atenolol) or thiazide diuretics [16].

However, the persistence of enlargement in mandibular anteriors and abscess in molar area advocated the need for local drug delivery in anterior regions and open flap debridement in the molar areas respectively. Thus, Metronidazole gel (Dr Reddy's Metrohex gel, a combination of o.25% w/w Chlorhexidine Gluconate and 1% w/w Metronidazole) was delivered into the inflamed gingival tissues as an adjunct to scaling and root planing resulting in complete resolution of inflammation and gingival enlargement and barring the need for invasive surgical intervention.

Metronidazole is a 5-nitroimidazole compound and one of the most common broad-spectrum antibiotics that has been proved to be efficacious as an adjunct to scaling and root planing. The rationale for choosing metronidazole is its bactericidal activity against gram positive and gram negative obligate anaerobic organisms. The compound acts by disrupting the synthesis of bacterial DNA in conditions with a low redox potential [17]. Upon entering the putative pathogens, it is reduced at the 5-nitro position resulting in a continuous concentration gradient, thereby allowing the diffusion of additional metronidazole into the cell and production of cytotoxic free radicals which are responsible for cell death [18]. Another reason is that it provides high degree of efficacy and relatively few adverse side effects [17]. Pavio M, et al. (2004), Pandit N, et al. (2013), Singh HP et al. (2016) etc in their studies have also demonstrated the efficacy of metronidazole gel as an adjunct to SRP in treating various periodontal infections [18].

On the contrary, Chlorhexidine gluconate is a bisbiguanide antiseptic that is considered to be the gold standard antiplaque agent [19]. The wide spectrum of antimicrobial activity encompasses gram-positive bacteria, gram-negative bacteria, yeasts and some lipophilic viruses. It is bacteriostatic at low concentration and bactericidal at high concentrations [20]. Dicationic positively charged chlorhexidine molecule attracts to the negatively charged bacterial cell wall causing the alteration of the integrity of the bacterial cell membrane and thus, chlorhexidine is attracted to the inner cell membrane where it binds to the phospholipids causing leakage of low molecular weight compounds like potassium ions. This leads to coagulation and precipitation of the cytoplasm causing the initiation of bactericidal stage [19].

Pardeep AR, et al. (2012) [21], Acharya P, et al. (2019) [22] etc. concluded that local drug delivery of combination of chlorhexidine and metronidazole in conjunction with SRP showed superior results in treatment of periodontal diseases.

It can be postulated that the severity of gingival enlargement in patients on these categories of medications correlates well with poor plaque control and is commensurate with the degree of plaque induced inflammation. Therefore, the importance of dental plaque as a cofactor in the etiopathogenesis of drug-induced gingival enlargement has also been recognized in the most recent classification system for periodontal disease.

CONCLUSION

The three types of pharmacological agents namely anticonvulsants, calcium channel blockers and immunosuppressants have been reported to result in gingival enlargement in genetically susceptible individuals. The histopathologic picture of the gingival connective tissue in response to these agents is uniformly characterized by an increment in the amount of collagen

fibers as well as noncollagenous proteins. The primary treatment usually focusses on drug substitution or withdrawal and meticulous plaque removal by means of non-surgical approach. However, because of the inefficiency of scaling and root planing in the inaccessible areas, local drug delivery at the target site proves to be advantageous as an adjunct to conventional therapy.

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