CASE REPORT

Drug Induced Gingival Overgrowth with Low-Dose Amlodipine: A Clinical Report

Swyeta Jain Gupta, Rohit Madan and Rajesh Jhingran

ABSTRACT

Aim: This case report demonstrates a satisfactory clinical response achieved by the periodontal treatment alone without a change in associated drug.

Summary: Gingival overgrowth is frequently observed as an unwanted side effect of certain systemic drugs given for non-dental treatment. It is being reported with three main groups of drugs as calcium channel blockers (CCBs), immunosuppressants, and anticonvulsants. Amlodipine, a third generation calcium channel blockers, have been studied to promote gingival overgrowth, although very few cases have been reported. This can have a significant effect on the quality of life as well as increasing the oral bacterial load by generating plaque retention sites. The management of gingival overgrowth seems to be directed at controlling gingival inflammation through a good oral hygiene regimen. However in severe cases, surgical excision is the most preferred method of treatment, followed by meticulous oral hygiene procedures.

Keywords: Calcium channel blocker, drug-induced gingival overgrowth, matrix metalloproteinases, tissue inhibitor of metalloproteinases (TIMP).

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INTRODUCTION

Drug-induced gingival overgrowth (DIGO) was first reported in 1939 by Kimball with chronic usage of the antiepileptic drug phenytoin.[1] Drugs associated with gingival overgrowth can be broadly categorized into three major groups according to their therapeutic actions, namely, anticonvulsants, immunosuppressants, and calcium channel blockers.[2] Ellis *et al*.[3] first reported gingival sequestration of amlodipine and amlodipine-induced gingival overgrowth. Amlodipine, a third generation dihydropyridine calcium channel blocker that is used in the management of both hypertension and angina.

Recently, gingival hyperplasia has been reported in patients receiving 10 mg per day of amlodipine within two months of onset. There are limited data on reports of hyperplasia with amlodipine at a dose of 5 mg, even after taking it for more than 6 months.[4] The prevalence of DIGO in patients taking amlodipine was reported to be 3.3% that is lower than the rate in patients taking nifedipine (47.8%).

The clinical features of DIGO usually presented as enlarged interdental papillae and resulting in a lobulated or nodular morphology. The effects are more commonly found in the anterior region and are limited to marginal and attached gingiva. Histologically, in nifedipine-induced gingival overgrowth it was described as the thickening of the spinous cell layer, slight to a moderate hyperkeratosis, fibroblastic proliferation and fibrosis of lamina propria. In the current case report, DIGO in patient taking amlodipine for the treatment of hypertension is presented. The management consists of oral hygiene procedures and surgical gingivectomy.

CASE REPORT

A 38-years old Indian woman reported to the Department of Periodontology with the chief complaint of swollen gingiva in the upper and lower front tooth region since several months. She felt very uncomfortable as the swelling was accompanied with spontaneous bleeding. She had hypertension since 5 years and under regular medication since 2 years and was taking Amlodipine 5 mg, Metoprolol 100 mg and Lovastatin to cholesterol control daily. She looked well and alert. Intraorally, there was gingival

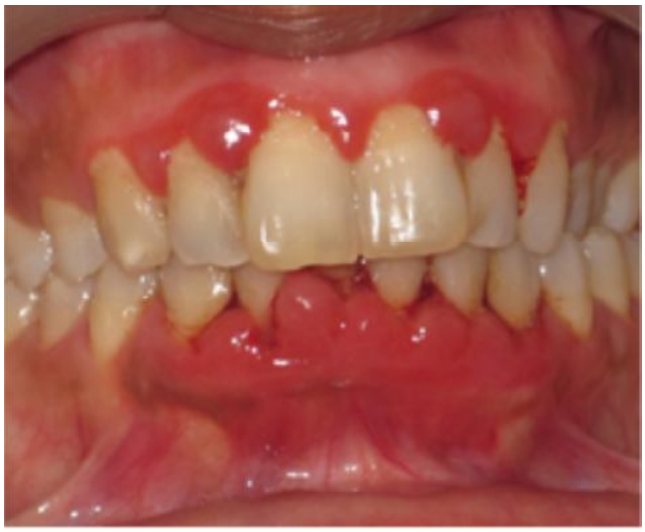

Figure 1: Intraoral picture showing the gingival overgrowth at the initial appearance

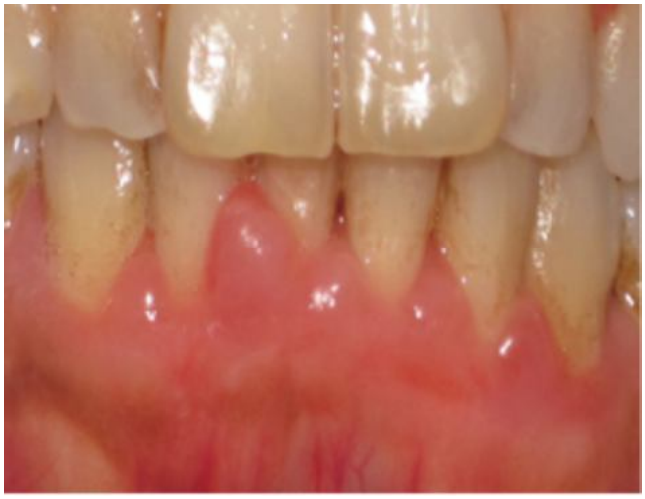

Figure 2: Gingival overgrowth appearance after non-surgical therapy

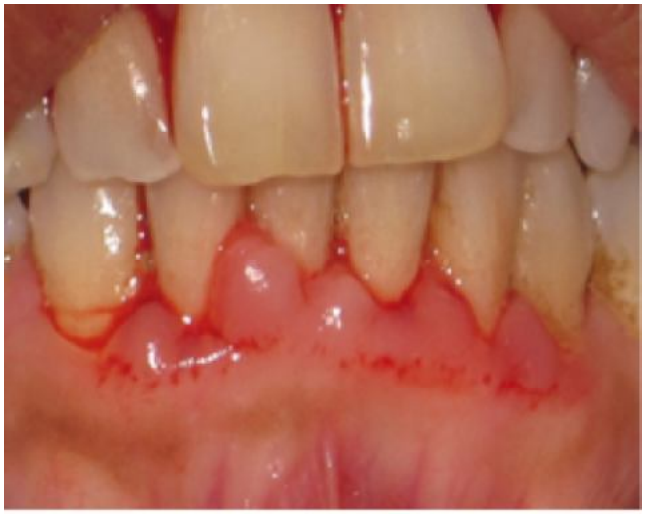

Figure 3: Bleeding points showing pseudo-Pocket depth

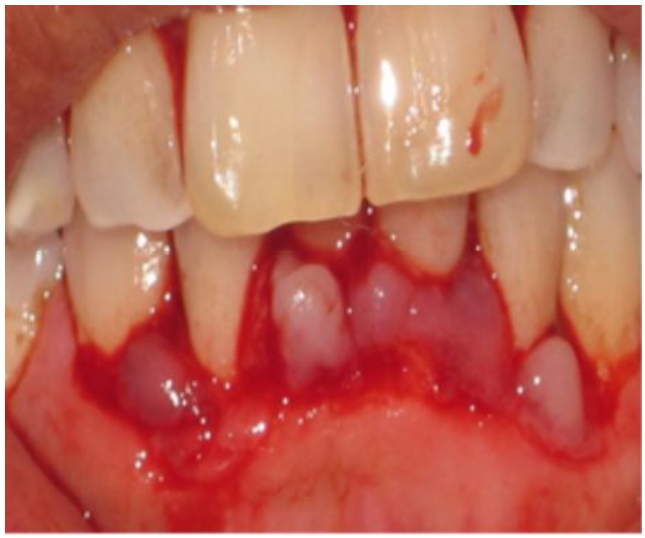

Figure 4: Surgical gingivectomy treatment on the lower labial gingiva

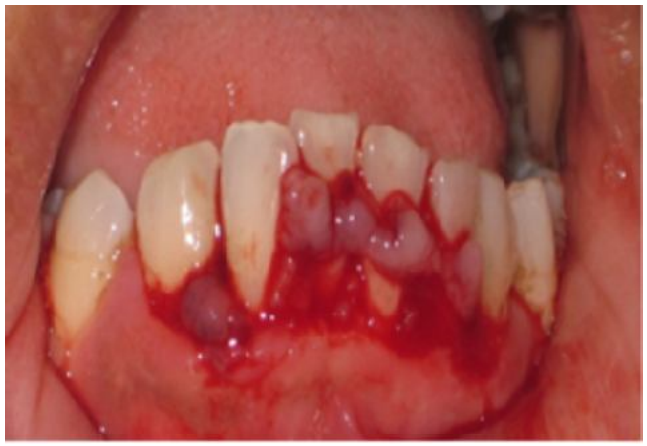

Figure 5: Gingivectomy tissue being removed

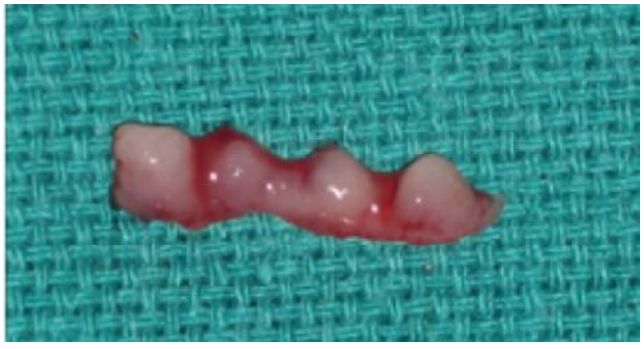

Figure 6: Exised gingivectomy tissue

overgrowth on the labial surface of the upper and lower teeth. The interdental papillae were inflamed and lobulated in appearance mainly at the lower anterior teeth. Her oral hygiene was very poor with abundant plaque and calculus. Bleeding on probing was present in all affected areas. The

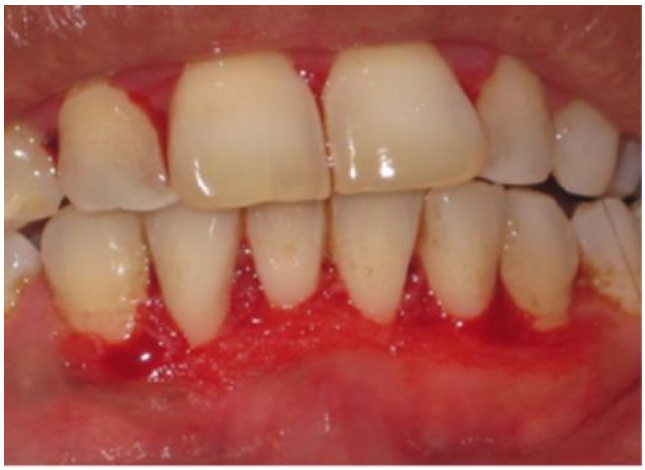

Figure 7: Aspect of the surgical wound at conclusion of the surgical procedure

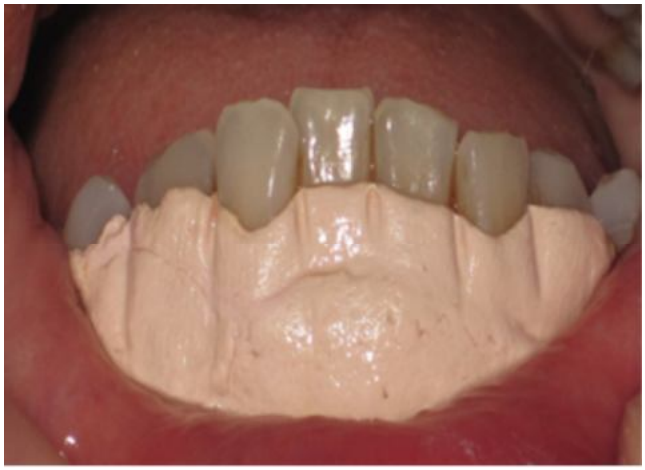

Figure 8: Coe-pak applied

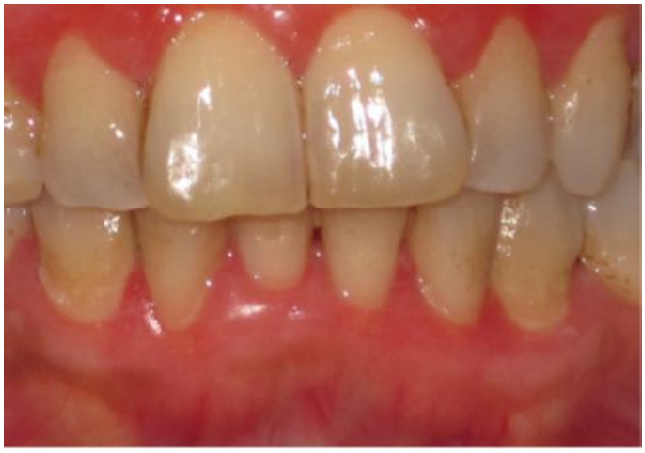

Figure 9: Gingival overgrowth had disappeared after 2 month of surgery

lack of periodontal pockets (mean probing depth: 2.4 mm, was a prominent feature of gingival overgrowth indicating an outward rather than vertical enlargement of gingiva. Gingiva was red in colour depicting gingival inflammation. Based on drug history and clinical examination of the patient provisional diagnosis of combined gingival enlargement was made. Complete hemogram of the patient was done, and all the parameters were within the normal range.

Full mouth scaling and root planing of was done, and patient was given oral hygiene instruction and motivation at the first visit. Review after one week revealed some reduction of the DIGO particularly in the maxillary arch. At the recall visit, surgical gingivectomy was performed for the overgrowth in the mandibular arch. The tissue overgrowth was resected using no.15 blade. All procedures were carried out under local anaesthesia (2% lignocaine with 1:200000 adrenaline). Patient was prescribed tablet Ibuprofen for three days and mouthwash chlorhexidine gluconate 0.2% for two weeks after each surgical procedure.

The periodontal dressing was removed 2 weeks post-operatively; overall the healing was satisfactory (Fig. 9). Patient was motivated to maintain a good oral hygiene. Surgical site was asymptomatic, when she last reported 2 months for follow-up, and has been reinstructed to maintain meticulous oral hygiene at subsequent visit.

DISCUSSION

The treatment of DIGO is still largely limited to the maintenance of an improved level of oral hygiene and surgical removal of the overgrown tissue as the pathogenesis is uncertain. There are numerous factors that may influence the relationship between the drugs and gingival tissues including age, genetic predisposition, pharmacokinetic variables, alteration in gingival connective tissue homeostasis, histopathology, ultrastructural factors, inflammatory changes and drug action on growth factors.5 Most studies show an association between the oral hygiene status and the severity of DIGO. This suggests that plaque-induced gingival inflammation may be important risk factor in the development and expression of the gingival changes.[6] In the present case the local environmental factors such as poor plaque control at the initial presentation may act as the risk factor that had contributed to worsening the existing gingival enlargement and, therefore, complicate the oral hygiene procedures. There was some reduction of the overgrowth observed particularly in the maxillary arch after the initial therapy was advocated.

The underlying mechanism behind DIGO involves inflammatory and non-inflammatory pathways. The proposed non-inflammatory mechanisms include defective collagenase activity due to decreased uptake of folic acid, blockage of aldosterone synthesis in an adrenal cortex, and consequent feedback increase in adrenocorticotropic hormone level and up-regulation of keratinocyte growth factor. Alternatively, inflammation may develop as a result

of direct toxic effects of concentrated drug in gingival crevicular fluid and/or bacterial plaque. This inflammation could lead to the up-regulation of several cytokine factors such as transforming growth factor-β1.[7-9]

Many studies have been conducted which showed that amlodipine cannot induce gingival hyperplasia at 5 mg once daily dose even if taken for more than 6 months. It can be caused only at a dose of 10 mg/day.[5,10] In contrast, the present case reported that 5 mg/day doses of amlodipine caused gingival hyperplasia. The mechanism through which these drugs induce gingival enlargement is still poorly understood. Amlodipine is a calcium channel blocker often prescribed for hypertension and it has been found that calcium channel blockers inhibit the intracellular Ca^{2+} uptake thereby stimulating gingival fibroblasts. It works on voltage-dependent calcium channels that are found in excitable cells (mainly neurons and muscle). These channels are normally closed at resting stage, but when activated, they open, allowing Ca2+ entry into the cell, leading to muscle activation. Calcium channel blockers, like amlodipine, inhibit calcium ion influx across the cell membrane of cardiac and smooth muscle cells, thus preventing ATPase, a calcium dependent enzyme, from breaking down APT and consuming energy. This reduces muscle contraction and neuron excitation. As a result, smooth muscles and myocardium relax, decreasing vascular resistance, which decreases blood pressure.

Also, not all the patients receiving the same drug develop gingival enlargement. Alternate reason can be that individuals with gingival enlargement have fibroblasts with an abnormal susceptibility to the drug. It has also been proposed that the susceptibility to pharmacologically induced gingival enlargement may be governed by existence of differential proportions of fibroblast subset in each that exhibit a fibrogenic response to these medications. It has also been shown that the functional heterogenicity exists in gingival fibroblasts in response to various stimuli.[11] 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 pro-inflammatory cytokine) in inflamed gingival tissues. Interleukin-6 also plays a role in fibrogenic responses of gingiva to these medications. Interleukin-6 targets fibroblasts which trigger the proliferation of fibroblasts and exert the positive regulation on collagen and glycosaminoglycans synthesis. So this cytokine has been proposed to play a pathogenic role in fibrotic gingival enlargement. There is a strong correlation between the production of inactive collagenase and responding fibroblasts. Because of reduced folic acid uptake, there is limited production of activator protein that converts inactive collagenase to active collagenase. Limited amount of collagenase becomes available.[5] Treatment consists of stopping the offending drug if possible with the physician's consent and providing the supplements of folic acid and ascorbic acid. Reduction in the size of the gingival overgrowth has been reported within a week of drug withdrawal and may lead to full resolution.[12] Patients benefit from effective oral hygiene measures, professional tooth cleaning, scaling, and root planing.[13]

Two main genes and their associated proteins involved in DIGO: permeability glycoprotein (P-gp) and human leukocyte antigen. Also, calcium antagonists act as inhibitors of the drug transporter permeability glycoprotein (P-gp).[14] P-gp is a well-characterized ATP-binding cassette transporter. These are trans-membrane proteins that use ATP hydrolysis to perform movement of substrates across intra- and extracellular membranes, thus giving this pump influence on the concentration of these drugs intracellularly. This is, most likely, a defense mechanism against harmful substances, regulating the distribution and bioavailability of drugs. Because the multidrug resistance 1 (MDR1) gene may modify P-gp expression, MDR1 polymorphisms was analyzed as a risk factor for gingival overgrowth induced by calcium channel blockers. The MDR1 polymorphisms when compared to P-gp expression in the endothelial layers of blood vessels obtained from healthy or inflamed gingiva, linked a genetic susceptibility to the drug transporter permeability glycoprotein (P-gp) that is inhibited by the calcium gradient effecting DIGO drugs.[15]

The human leukocyte antigen system (HLA) is the name of the major histocompatibility complex in humans. Its genetic variability has also been associated with susceptibility to DIGO. Thomason *et al*. using stepwise regression analysis identified HLA-B37 genotype as positively associated with DIGO.[16,17]

Kato *et al*.[18] made several key conclusions about the molecular mechanism of DIGO. This accumulation of collagen was not the result of an overexpression of collagen; on the contrary, it was due to a decrease in collagen phagocytosis and degradation; due to slowing down of both the processes involved in collagen fibrils degradation; (extracellularly) via secretion of collagenase (matrix mellatoproteinases) and intracellularly involving phagocytosis by fibroblasts. He also shows that TNF-α, a potent inflammatory mediator, synergistically adds to the pharmacological effects of drug, thus proving that inflammation magnifies the effects of the DIGO medications. However, it must be kept in mind that this is an in vitro study, and in vivo results vary. Not every patient reacts to the drugs with DIGO. There is a wide range of genes and proteins that play a role in DIGO as well, leaving some people more susceptible than others. However, according to the currently accepted theory DIGO is due to an excess in collagen and ground substance in the extracellular space, and that this is due to the fibroblasts inability to breakdown the available substrates.

In order for fibroblasts to adhere and phagocytose the extracellular matrix components, their transmembrane cells' surface receptors must first recognize the collagen. These surface receptors are called integrins, which are responsible for the proliferation of the cell, response to growth factors, and prevention of cell death. Cells with alpha-2-beta1 preferentially adhere to the type I collagen, the main constituent of gingiva. Interestingly, alpha-2-beta-1 integrin-mediated collagen phagocytosis is regulated by intracellular calcium, and DIGO medications' alteration of intracellular calcium disturbs this mechanism.

The 807C gene encodes for the alpha-2 subunit of the alpha-2-beta-1 integrin protein. It was proved that the expression of alpha2 integrin 807 T/C polymorphism correlates with drug-induced gingival overgrowth.[6] Hence it was found that the 807C gene allele is one of the genetic risk factors for DIGO because it leads to less alpha2-beta1 integrin expression on fibroblasts. This leads to decreased binding to type I collagen, therefore allowing for less phagocytosis and more residual extracellular collagen. Proteinases used to remodel the gingival matrix can be divided into extracellular or intracellular categories. Maxtrix metalloproteinases are extracellular enzymes that destroy proteins mainly in inflammatory states.[19]

In contrast, the cathepsins are proteases found in intracellular lysosomes.[20] They are used during fibroblast phagocytosis in normal matrix turnover. Importantly, cathepsin substrates include collagen. At least two transcript variants encoding the same protein have been found for this gene. In humans, it is encoded by the cts-l gene.[21] Nishimura proved the role of the cts-l gene and its product, the cathepsin-L enzyme, in producing the clinical signs associated with DIGO in a rat model.

Also, fibroblast remodeling of the extracellular matrix requires binding of the cell to the proteins for phagocytosis. Intracellularly, fibroblasts contain cathepsins for protein phagocytosis. If these cathepsins are altered, phagocytosis will suffer. Extracellularly, protein degradation of matrix proteins occurs with MMP and is regulated by tissue inhibitor of metalloproteinases (TIMP). MMP-1, a potent collagenase, is of special consideration in DIGO. Yamada et al.[21] concluded that there was a suppression of the expression of MMP-1, TIMP-1, and cathepsin-L. He showed that matrix degradation depression was due to a reduction in not only intracellular remodeling, but extracellular remodelling mechanisms as well (MMP-1). Similar in vitro suppressive levels has also been shown for MMP-3.[22]

It has been shown that expression of CCN2, also known as connective tissue growth factor (CTGF), correlates positively with the degree of gingival fibrosis, and that markers of epithelial to mesenchymal transition (EMT) are characteristic of all drug-induced forms of gingival overgrowth. Also, drug induced gingival overgrowth tissues exhibit marked discontinuities in basement membranes. Disrupted basal membrane structure in gingival overgrowth tissues is accompanied by a discontinuous collagen type IV expression pattern and decreased laminin.[5,25]

These findings provide new additional support for the hypothesis that epithelial plasticity and EMT promote gingival overgrowth, resulting in compromised basal membrane structure and increased interactions between epithelial and connective tissue layers that contribute to fibrotic pathology. These findings lend further experimental support to the notion that epithelial plasticity and EMT contribute to the development of drug-induced gingival overgrowth.

Mast cells have become a recent concern in drug-induced gingival overgrowth (DIGO), an unwanted outcome of systemic medication. Most of the studies have confirmed the significant presence of inflammation as a prerequisite for the overgrowth to occur. The inflammatory changes within the gingival tissue appear to influence the interaction between the inducing drug and the fibroblast activity. Mast cells participate in many inflammatory oral diseases, particularly those associated with fibrosis. They possess very diverse roles ranging from proinflammatory to immunomodulatory. Upon their activation, they promote the local RAS generation consequently able to stimulate endothelium and other profibrotic mediators.

In the present case report, gingival overgrowth was satisfactorily treated via initial periodontal therapy including oral hygiene instruction and motivation, followed with surgical gingivectomy treatment. Therefore, patient must be informed of this tendency and the importance of maintenance of an effective oral hygiene as key factors in preventing and managing gingival overgrowth associated with this drugs. It was also concluded that gingival hyperplasia could be a side effect of amlodipine even with a very short term and low dose administration (5 mg). Henceforth, the physicians and dentists should be aware of the etiologic medications that can induce gingival hyperplasia and be able to identify changes in the oral cavity in such patients to prevent, diagnose, and successfully manage them. A cooperative teamwork between the patient, his physician, and the dental health care professional is mandatory to minimize and successfully treat such unwanted side effects of drugs. However, supportive followed up is necessary for an effort to monitor her gingival/periodontal status, to assess and reinforce oral hygiene and to periodically provide professional care to prevent the recurrence of GO.

REFERENCES

1. Pradhan S, Mishra P. Gingival enlargement in antihypertensive medication. J Nepal Med Assoc 2009; 48: 149-52.
2. Dongari-Bagtzoglou A. Drug-associated gingival enlargement. J Periodontol 2004; 75: 1424-31.
3. Ellis JS, Seymour RA, Steele JG, Robertson P, Butler TJ, Thomason JM. Prevalence of gingival overgrowth induced by calcium channel blockers: a community-based study. J Periodontol 1999; 70: 63-7.
4. Jorgensen MG. Prevalence of amlodipine-related gingival hyperplasia. J Periodontol 1997; 68: 676-8.
5. Seymour RA, Thomason JM, Ellis JS. The pathogenesis of drug-induced gingival overgrowth. J Clin Periodontol 1996; 23 (3 pt1): 165-75.
6. Barclay S, Thomason JM, Idle JR, Seymour RA. The incidence and severity of nifedipine induced gingival overgrowth. J Clin Periodontol 1992; 19: 311-4.
7. Nyska A, Shemesh M, Tal H, Dayan D. Gingival hyperplasia induced by calcium channel blockers: mode of action. Med Hypotheses 1994; 43: 115-8.
8. Marshall RI, Bartold PM. A clinical review of drug induced gingival overgrowths. Aust Dent J 1999; 44: 219-32.
9. Lafzi A, Farahani RM, Shoja MA. Amlodipine induced gingival hyperplasia. Med Oral Patol Oral Cir Bucal 2006; 11: E480-2.
10. Triveni MG, Rudrakshi C, Mehta DS. Amlodipine induced gingival overgrowth J Indian Soc Periodontol 2009; 13: 160-3.
11. Seymour RA. Calcium channel blockers and gingival overgrowth. Br Dent J 1991; 170: 376–9.
12. Raman PG, Mishra VN, Singh D. Nifedipine induced gingival hyperplasia. J Assoc Physicians India 1988; 36: 231-3.
13. Mavrogiannis M, Ellis JS, Thomason JM, Seymour RA. The management of drug-induced gingival overgrowth. J Clin Periodontol 2006; 33: 434-9.
14. Eichelbaum M, Fromm MF, Schwab M. Clinical aspects of the MDR1 (ABCB1) gene polymorphism. Ther Drug Monit 2004; 26: 180–5.
15. Meisel P, Giebel J, Kunert-Keil C, Dazert P, Kroemer HK, Kocher T. MDR1 gene polymorphisms and risk of gingival hyperplasia induced by calcium antagonists. Clin Pharmacol Ther 2006; 79: 62–71.
16. Thomason JM, Seymour RA, Ellis JS, Kelly PJ, Parry G, Dark J, *et al*. Determinants of gingival overgrowth severity in organ transplant recipients: an examination of the role of the HLA phenotype. J Clin Periodontol 1996; 23: 628–34.
17. Cebeci I, Kantarci A, Firatli E, Carin M, Tuncer O. Evaluation of the frequency of HLA determinants in patients with gingival overgrowth induced by cyclosporine A. J Clin Periodontol 1996; 23: 737–42.
18. Kato T, Okahashi N, Kawai S, Kato T, Inaba H, Morisaki I, *et al*. Impaired degradation of matrix collagen in human gingival fibroblasts by the antiepileptic drug phenytoin. J Periodontol 2005; 76: 941–50.
19. Ogino M, Kido J, Bando M, Hayashi N, Wada C, Nagata T, *et al*. α2 integrin +807 polymorphism in drug-induced gingival overgrowth. J Dent Res 2005; 84: 1183–6.
20. Roth W, Deussing J, Botchkarev VA, Pauly-Evers M, Saftig P, Hafner A, *et al*. Cathepsin L deficiency as molecular defect of furless: hyperproliferation of keratinocytes and pertubation of hair follicle cycling. Embo J 2000; 14: 2075–86.
21. Joseph LJ, Chang LC, Stamenkovich D, Sukhatme VP. Complete nucleotide and deduced amino acid sequences of human and murine pre-procathepsin L. An abundant transcript induced by transformation of fibroblasts. J Clin Invest 1988; 81: 1621–9.
22. Yamada H, Nishimura F, Naruishi K, Chou HH , Takashiba S, Albright GM, *et al*. Phenytoin and cyclosporin A suppress the expression of MMP-1, TIMP-1, and cathepsin L, but not cathepsin B in cultured gingival fibroblasts. J Periodontol 2000; 71: 955–60.
23. Kataoka M, Shimizu Y, Kunikiyo K, Asahara Y, Yamashita K, Ninimiya M, *et al*. Cyclosporin A decreases the degradation of type I collagen in rat gingival overgrowth. J Cell Physiol 2000; 182: 351–8.
24. Kantarci A, Black SA, Xydas CE, Murawel P, Uchida Y, Yucekal-Tuncer B, *et al*. Epithelial and connective tissue cell CTGF/CCN2 expression in gingival fibrosis. J Pathol 2006; 210: 59-66.
25. Norrby K. Mast cells and de novo angiogenesis: *angiogenic* capability of individual mast-cell mediators such as histamine, TNF, IL-8 and bFGF. Inflamm Res 1997; 46 Suppl 1: S7-8.