Gingival hyperplasia: Should drug interaction be blamed for?

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Abstract:
Gingival overgrowth (GO) is one of the common findings in clinical practice. There could be several causes including drugs associated with the GO. Carbamazepine (CBZ) and amiodipine are the drugs which are infrequently documented as a cause in inducing the gingival hyperplasia. Certain drugs in the body fluid might limit the population of plaque bacteria and alter their metabolism that in turn induce the inflammatory mediators and also activate the genetic and biochemical factors responsible for gingival fibroblast growth. Drug-induced GO is a side effect with a multifactorial etiology that seems to orchestrate the interaction between drugs and fibroblasts in the gingiva. We describe a case of trigeminal neuralgia with hypertension treated with multiple drugs including amiodipine and CBZ. Although amiodipine is known to be infrequently associated with GO, an association of CBZ with GO is even rarer. Causality analysis on the World Health Organization Uppsala Monitoring Centre’s scale indicates a probable association with offending drugs.

Keywords:
Amlodipine, carbamazepine, gingival overgrowth, pharmacovigilance

Introduction
Gingival overgrowth (GO) secondary to systemic medication use includes the administration of drugs such as antiepileptics, immunosuppressants, and calcium channel blockers. GO is characterized by the accumulation of collagenous components in the extracellular matrix of gingival connective tissues accompanied by varying degrees of inflammation. The GO cannot be explained wholly by the mechanism of the intended pharmacological action of the drug. The identified risk factors associated with GO are age and sex of the patient, type of medication, genetic factors, and the inflammatory status of the periodontal tissues due to oral hygiene. Prevalence of drug-induced gingival hyperplasia varies widely and has been very scarce. Phenytoin-induced GO is the well-documented entity in the scientific literature. However, it may also be associated rarely with the chronic use of other antiepileptics.

Case Report
A 43-year-old premenopausal woman presented to the dental outpatient department with pain and swelling in the gingival region. For trigeminal neuralgia, she was on various oral medications, namely, carbamazepine (CBZ), amitriptyline, clonazepam, tizanidine, and tramadol (as and when required) for the past 2 years. Three months back, she was diagnosed to have hypertension and was put on oral amlodipine 5 mg once a day.

For the past 2 months, she was having the pain of increasing intensity with gradually enlarging gingival swelling. The lesions were inflamed, mulberry shaped, firm, and reddish, with...
lobulated surface and no tendency to bleed [Figure 1]. Amlodipine was replaced with olmesartan and was advised chlorhexidine mouthwash for regular use. Her blood parameters were within normal limits. On the follow-up visit after 2 weeks, she informed that her swelling and symptoms have lessened [Figure 2]. She continued with the chlorhexidine mouthwash along with other medications. Fifteen days later, she turned up with similar complaints of pain and swelling [Figure 3]. It was learned that tablet fluoxetine was substituted for amitriptyline by her physician. Fluoxetine was stopped and the patient was advised to continue the remaining drugs. In view of the patient’s drug history, a possibility of the drug-induced GO was considered.

**Discussion**

The prevalence of drug-induced gingival hyperplasia varies according to the type of medication, but the clinical and microscopic appearance of the lesion is similar. The presence of plaque and gingival inflammation appears to exacerbate GO irrespective of the initiating drug.\(^3\) Certain drugs in the body fluid might limit the population of plaque bacteria or may alter their metabolism. Drug-induced changes in the plaques in turn induce the inflammatory mediators and also activate the genetic and biochemical factors which are responsible for gingival fibroblast growth.\(^3\) The existence of differential proportions of fibroblast subsets in an individual might have a proliferative effect when stimulated by the various factors initiated by the drugs.\(^3\) Interleukin-1 beta (IL-1\(\beta\)) and IL-6 are pro-inflammatory cytokines which enhance the proliferation of fibroblasts by controlling collagen and glycosaminoglycan synthesis.\(^3\)

Drugs may interfere with the synthesis and function of collagenases that disrupt basal membrane structure and may promote epithelial plasticity and epithelial-to-mesenchymal transition and thus contribute to fibrotic pathology of GO tissues.

A genetic predisposition could also influence and trigger the variety of factors in the drug plaque-induced inflammation which might promote gingival fibroblast functional heterogeneity, collagenolytic activity, drug metabolism, and impair collagen synthesis.

The patient in our case noticed pain and gingival swelling following the initiation of amlodipine, which is known to cause gum enlargement.\(^4\) We suspected that amlodipine alone could possibly be related to the first episode of GO. CBZ though rarely associated with GO may also be viewed as a contributory agent. This assumption is based on the fact that addition of amlodipine could have resulted in increased CBZ serum levels.\(^5\) Thus, the combined role of CBZ and amlodipine cannot be completely ruled out. Our assumption was further substantiated by the gradual decrease in gingival swelling after substitution of amlodipine with olmesartan.
The rapid onset of the second episode of pain and swelling following fluoxetine administration could be firstly due to incomplete resolution of the first episode and secondly due to raised CBZ serum levels by fluoxetine. The severity of GO tends to be associated with higher drug levels in gingiva, and there exists a good correlation between CBZ concentrations in the plasma and saliva.\(^6\) Fluoxetine is a substrate for CYP3A4 and may also compete with CBZ for metabolism.\(^7\) On both occasions, an increased plasma level of CBZ could not be confirmed. However, the patient did not mention any adverse effect that could be ascribed to CBZ.

The patient is gradually improving continuing with her treatment for trigeminal neuralgia and hypertension. In this interesting case, we suspect that increased CBZ levels secondary to drug interaction could possibly have resulted in the flare-up of the incompletely resolved lesion. An analysis by the World Health Organization Uppsala Monitoring Centre\(^8\) causality scale indicated that the first episode of GO was probably associated with amlodipine (withdrawal led to a reduction in symptoms) whereas the second episode possibly to CBZ (secondary to raised serum levels as the reaction occurred within the reasonable time frame to the administration of interacting drug, i.e., fluoxetine).

**Conclusion**

One should try to rule out the possibility of drug interaction, especially in the setting of multidrug therapy as a cause for presenting drug-related effects. Drug-induced GO is a side effect with a multifactorial etiology. It is the inflammatory changes that seem to orchestrate the interaction between drugs and fibroblasts in the gingiva. Dental surgeons need to discuss this issue with their medical colleagues and to practice due care while prescribing the drugs associated with GO. A close monitoring is warranted to detect the GO at the earliest to that offending agent may be removed or substituted. Thus, knowledge of pharmacovigilance is important to all health-care professionals including dentists to diagnose any adverse drug-related effects. On the other hand, alternative safer drug regimens may always be tried that are better tolerated and are less likely to be associated with such side effects.

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**Conflicts of interest**

There are no conflicts of interest.

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