

# GINGIVAL HYPERPLASIA: AN INTRA-ORAL SIDE EFFECT OF PHENYTOIN, NIFEDIPINE AND CYCLOSPORINE THERAPIES.

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## SYNOPSIS

Drug-induced gingival hyperplasia has been observed commonly with phenytoin. Lately, this was reported with two relatively new drugs ie. nifedipine and cyclosporine. Phenytoin is an anti-convulsant drug used for the treatment of grand mal and psychomotor epilepsy. Nifedipine is used to treat angina and ventricular arrhythmias. Cyclosporine is an immuno-suppressant used as an anti-rejection agent in organ transplants. The clinical and histological features of gingival hyperplasia together with a brief pharmacology of each drug is reviewed. Gingival hyperplasia induced by the three drugs is almost identical in clinical and histological features. Case management involves meticulous oral hygiene and elimination of gingival irritations.

*Keywords: Gingival hyperplasia, side effect of, phenytoin, nifedipine, cyclosporine.*

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## INTRODUCTION

Gingival hyperplasia may occur as a result of inflammation, fibrosis or a combination of both(1). Generalised inflammatory enlargement may occur due to a number of local and systemic conditions. However, fibrous enlargement is mainly due to idiopathic gingival fibromatosis or drug-induced. For a long time since 1939, phenytoin has been noted as the most common cause of drug-related enlargement(2). Recently, this has been observed to occur with two relatively new drugs too, namely, cyclosporine(cyclosporin-A) and nifedipine. Very rarely gingival hyperplasia has been reported in patients treated with anti-convulsants primidone(3), sodium valproate(4), mephenthoin(5) and phenobarbital(6).

This article reviews gingival hyperplasia induced by phenytoin, nifedipine and cyclosporine.

## PHENYTOIN

The principal pharmacological action of phenytoin (diphenylhydantoin, phenytoin sodium) is the depression of the motor cortex without appreciable effect upon the sensory regions(7). This drug has been used for the treatment of grand mal and psychomotor epilepsy for more than 40 years and still is the drug of choice(8). It can be used at full dosage for maximal anti-convulsant effect without causing a general central nervous system depression(9).

Various side effects have been noted with phenytoin therapy, the most common being anorexia, nausea, rash, hir-

sutism, ataxia, nystagmus, withdrawal seizures and gingival hyperplasia(7). Kimball(2) was the first report on gingival hyperplasia due to phenytoin.

Not all patients under phenytoin treatment developed gingival hyperplasia. The incidence varies from 0% to 84.5% and occurred more frequently in young individuals(10). In most patients, it develops 2 to 3 months after the start of therapy and peaks in severity after 12 to 18 months(11).

Clinically, the hyperplasia starts at the interdental papillae with occasional involvement of the gingival margins. Gradually the enlargement takes the form of coalescent lobulations extending labially or lingually with small clefts present between these lobulations. In the majority of cases, the hyperplasia is found in the anterior part of the mouth(12). The crowns of the teeth are partially covered by the hyperplastic gingiva and in severe cases the entire crown might be covered with gross displacement of the teeth(12). Hyperplasia rarely occurs in edentulous areas(13).

Uncomplicated cases of phenytoin-induced gingival hyperplasia present with a hard, firm, resilient and insensitive gingiva with little tendency to bleed. The surface has a normal pink colour, is stippled and has a granular or smooth appearance(12). If secondary inflammation is present, the tissue may become dark red, oedematous, spongy, friable, ulcerated and bleed easily with gingival enlargement(9). The clinical appearance of phenytoin-induced gingival enlargement is shown in Figure 1.

Histologically, there is a thickening of the squamous epithelium with a thin keratin layer present on the surface. There is some degree of acanthosis ie. the rete ridges/pegs becoming elongated, thinner, and tend to split at their ends(12). In the connective tissue, the changes are fibroblast proliferation and increased formation of collagen fibres. Also there is the presence of chronic inflammatory cells mainly lymphocytes and plasma cells (12). The histological appearance is shown in Figure 2.

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Figure 1 • Severe gingival hyperplasia in a 20-year old Indian female on phenytoin therapy for 6 years. Note the hyperplastic gingivae which cover about half the tooth crowns.

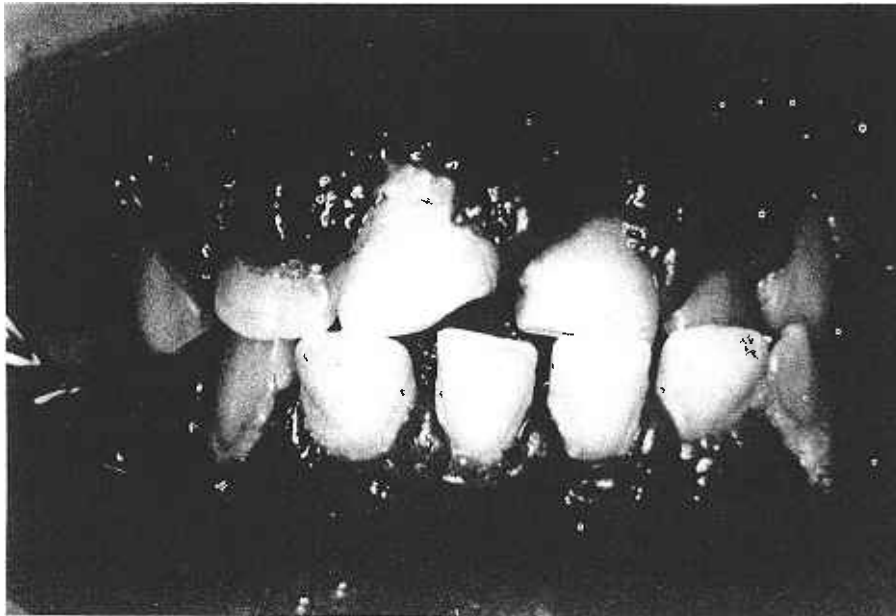
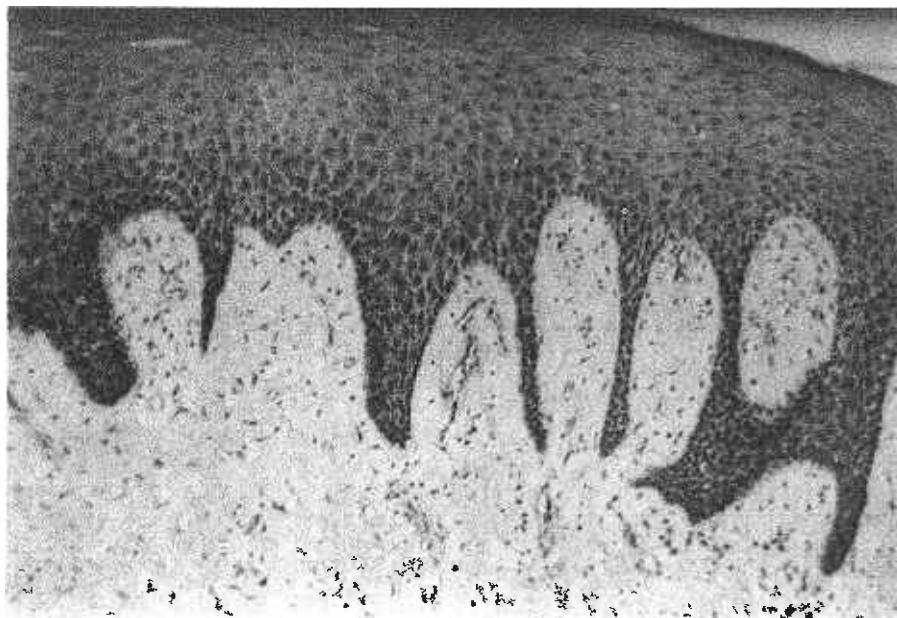


Figure 2 • Photomicrograph of phenytoin-induced gingival hyperplasia showing the thickened epithelial layer and the prominent rete pegs/ridges. (Hematoxylin and Eosin. X 100).



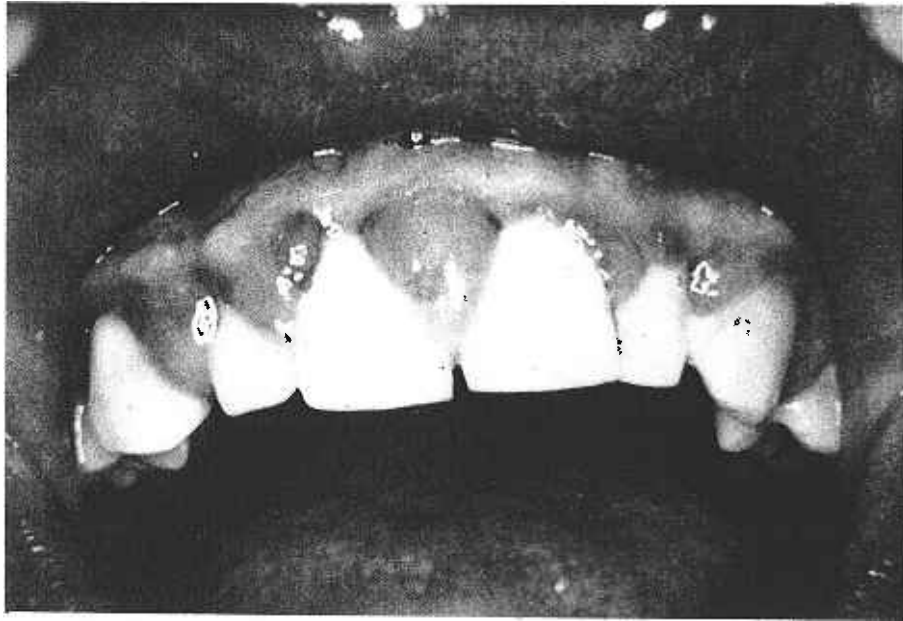


Figure 3 • Clinical photographs (upper and lower dental arches) of nifedipine-induced gingival hyperplasia in a 51-year old Malay male treated with the drug for 3 years. The swollen inter-dental papillae were firm and fibrotic.



## NIFEDIPINE

Nifedipine is a relatively new and increasingly used medication in the treatment of vasospastic angina, chronic stable angina and ventricular arrhythmias(14). It is as effective as oral nitrates and beta-adrenergic blocking agents in the treatment of chronic stable angina. Nifedipine is used to treat chronic stable angina only in patients refractory to, or cannot tolerate adequate doses of the above drugs(15).

Nifedipine acts by inhibiting the extracellular calcium influx across the membranes of cardiac and vascular smooth muscles without changing the serum calcium levels(14). This reduces the contractile process of the cardiac muscles thereby reducing the utilization of oxygen by the myocardium. Concurrently, the vascular smooth muscles of the main coronary and systemic arteries have their contractile process reduced too by nifedipine resulting in relaxation and prevention of coronary artery spasms(14).

Side effects and adverse reactions of this drug includes hypotension, headaches, weakness, muscles cramps, flushing, dizziness, tremour, joint stiffness, peripheral oedema, dermatitis, pruritus and urticaria(14). Recently, gingival hyperplasia has been observed to occur with this drug. So far, less than 10 cases have been reported in the literature (16,17,18) including the case illustrated here. These cases were first reported in 1984(16,19).

The clinical appearance of nifedipine-induced gingival hyperplasia is similar to the phenytoin-induced type(16). The hyperplasia appeared 1 to 2 months after the drug therapy and within a week after withdrawal of the drug, the

hyperplasia decreased with symptomatic improvement. Readministration exacerbated the condition again. A generalised, markedly lobulated enlargement of the facial and lingual gingivae was observed which seemed to originate interdentially and then spread across the tooth surfaces(16). The clinical appearance of nifedipine-induced gingival hyperplasia is shown in Figure 3.

Histologically, the gingival biopsy appearance is similar to that of phenytoin-induced hyperplasia ie. the presence of parakeratosis and thin elongated rete pegs/ridges in the epithelium with numerous fibroblasts in the connective tissue(16). An increase in the extra-cellular ground substance has also been noted(18). The histologic picture of the lesion is seen in Figure 4.

## CYCLOSPORINE

Cyclosporine (also known as cyclosporin-A) is a powerful immunosuppressant used in organ transplant procedures to prevent rejection. It has been used to treat type-I diabetes mellitus as well as to treat several other autoimmune disorders(20). Its immuno-suppressive effect is selective ie. only a specific component of the immune system is affected mainly the T-lymphocytes, leaving the humoral immune response intact(20).

A number of side effects have been observed with cyclosporine. These include nephrotoxicity, hepatotoxicity, mild anaemia, transient tremors, transient paraesthesias and excessive hair growth. Side effects involving the oral and perioral region include gingival hyperplasia and a transient perioral hyperaesthesia (20).

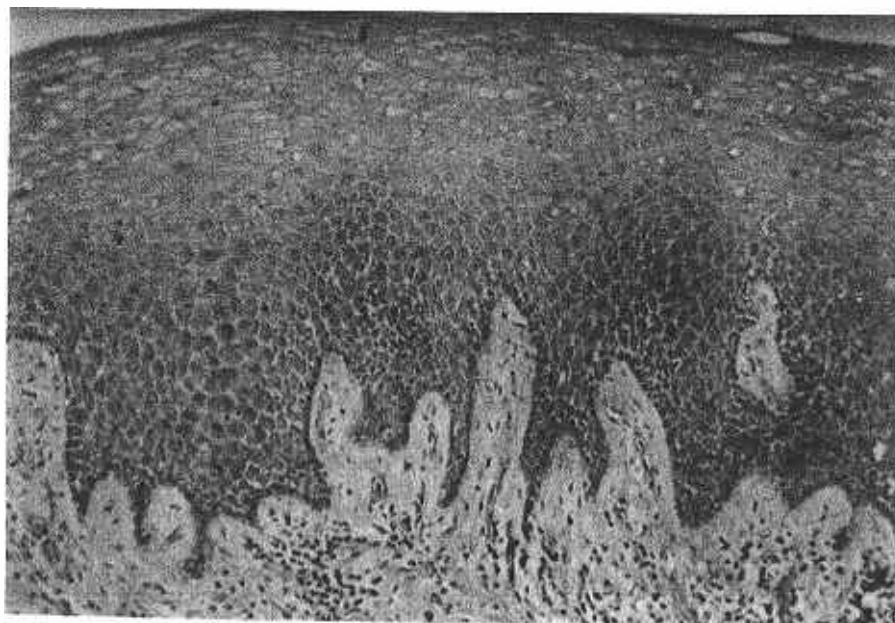


Figure 4 • Photomicrograph of nifedipine-induced gingival hyperplasia. Note the increase in thickness of the epithelium layer. (Hematoxylin and Eosin, X 100).

Gingival hyperplasia described as "gum hypertrophy" was first reported in 1979(21). Since then, a few more were reported in the dental literature (22,23,24). Clinically, the fibrous gingival hyperplasia is essentially similar in appearance, distribution and texture to phenytoin-induced gingival overgrowth(20,22,24). It is more commonly found on the labial than on the lingual surfaces and in the anterior region of the dental arch than the posterior. The hyperplasia is aggravated by poor oral hygiene, faulty dental restorations and mouth breathing(20).

Histologically, the predominant feature is the proliferation of collagen fibres in the connective tissue. There is also epithelial downgrowth deep into the connective tissue resembling that of phenytoin-induced gingival hyperplasia. The connective tissue is highly vascularised(22,23):

## DISCUSSION

The exact mechanism of the gingival hyperplastic reaction of the 3 drugs mentioned above is unknown. For phenytoin, tissue culture studies have shown a direct stimulatory effect on fibroblast proliferation and morphologic structure(25). Other factors implicated are local irritating factors (poor oral hygiene) which produce gingival inflammation(26). The inflammation causes mast cell degranulation in the gingival connective tissue which in turn stimulates the fibroblast to produce more collagen. Direct effect of phenytoin on mast cells has also been suggested(12).

Very little information is available at the moment on the

mechanism of hyperplasia induced by nifedipine and cyclosporine. These drugs may only act as cofactors in the mechanism as suggested for phenytoin. The 3 drugs are different structurally and gingival hyperplastic response may result from metabolic by-products rather than the drugs themselves(27). Similarly acting metabolites of all these drugs may be involved. Nifedipine and phenytoin have one property in common though i.e. the ability to alter calcium metabolism. It may be speculated that the gingival hyperplasia is related to altered calcium metabolism(17).

The gingival hyperplasia associated with the 3 drugs can be controlled and minimised though it may not be entirely preventable by maintaining a high standard of oral hygiene and eliminating other causes of gingival irritation such as calculus, faulty prosthesis and faulty restorations(20,22). The patient should be educated about the role of dental plaque in the aetiology of periodontal disease and as a factor in enhancing gingival hyperplasia. This is followed by scaling to remove supra and subgingival calculus. All these procedures should be carried out before the drug is instituted. Thus prior to drug therapy, the patient should be referred to a dentist or a periodontist for the necessary oral assessment and treatment.

If despite the above preventive measures severe gingival hyperplasia developed, gingivectomy or gingivoplasty could be carried out. The patients should be informed of the possibility of recurrence. Cessation, reduction and/or treatment with alternative drugs results in regression in most of the cases though not a complete one(16,20).

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