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The Hidden Impact of Medications: Unveiling Drug-Induced Gingival Overgrowth

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ABSTRACT

Drug-induced gingival enlargement (DIGO), previously termed drug-induced gingival hyperplasia, occurs as a side effect of certain systemic drugs. These drugs, primarily used for non-dental treatments, include anticonvulsants, immunosuppressants, and calcium channel blockers. DIGO manifests as firm, painless, nodular enlargements of the gingiva, particularly affecting the interdental papilla and can interfere with speech, chewing, and aesthetics. The pathophysiology involves inhibited calcium ion influx at the cellular level, with plaque-induced inflammation exacerbating the condition. Common causative drugs include phenytoin, cyclosporine, and nifedipine, each presenting distinct histological patterns. Phenytoin, for instance, is associated with a more fibrotic response, whereas cyclosporine triggers a more inflamed, vascular response. The condition is most prevalent in male children and adolescents, particularly in the anterior region.

Effective treatment includes improving oral hygiene, considering medication substitution, and in some cases, surgical intervention. Alternative medications such as tacrolimus for cyclosporine or diltiazem for nifedipine are recommended due to lower associated rates of gingival overgrowth. Non-steroidal anti-inflammatory drugs,

antibiotics, and folate supplementation are also part of the management strategy. The condition typically shows improvement 6 to 12 months after the discontinuation of the causative drug.

KEYWORDS: drug ,gingival enlargement, anticonvulsant.

The Hidden Impact of Medications: Unveiling Drug-Induced Gingival Overgrowth

INTRODUCTION

Drug induced gingival enlargement or gingiva overgrowth previously referred as drug induced gingiva hyperplasia occurs due to systemic drug use .Some drugs used for non dental treatment can cause gingival enlargement .The condition may create speech ,mastication ,tooth eruption,and esthetic problems. Predisposing factors that cause gingival overgrowth are age ,genetic predisposition ,pre existing plaque. Certain drugs used for treatment are anticonvulsants,immunosuppressants and calcium channel blockers .Drug Azithromycin has a capacity to improve gingival overgrowth in those who administrate drug cyclosporine A ,avoiding it's need to change the drug to another agent . (1)

PATHOPHYSIOLOGY

The drugs causing gingival enlargement have similar mechanism of action at the cellular level, where they inhibit intracellular calcium ion influx. The action of these drugs on calcium and sodium ion flux may prove to be the key in understanding why three dissimilar drugs

have a common side effect upon a secondary target tissue, such as gingival connective tissue. An appraisal of the various investigations into the pathogenesis of drug-induced gingival overgrowth supports the hypothesis that it is multi factorial . Plaque scores and gingival inflammation appear to exacerbate the expression of drug-induced gingival overgrowth, irrespective of the initiating drug. The severity of gingival enlargement in patients taking medications correlates well with poor plaque control and is commensurate with the degree of plaque induced inflammation. The importance of plaque as a cofactor in the etiology of drug-associated gingival enlargement 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. (2)

EPIDEMIOLOGY

Most commonly seen in male children and in adolescents in the anterior region.

Phenytoin(anticonvulsant drug) is the most common cause.(2)

Category	Pharmacologic agent
Anticonvulsants	Phenytoin
	Sodium valproate
	Phenobarbitone
	Vigabatrin
	Primidone
	Mephenytoin
	Ethotoin
	Ethosuximide
	Methosuxinimide
Immunosuppressants	Cyclosporin
	Tacrolimus
	Sirolimus
Calcium channel blockers	Nifedipine
	Nitrendipine
	Felodipine
	Nicardipine
	Manidipine
	Amlodipine
	Nimodipine
	Nisoldipine
	Verapamil
	Diltiazem

History

Patients experiencing Drug-Induced Gingival Overgrowth (DIGO) have a medical background that includes conditions like hypertension, angina, epilepsy, or recent organ transplants. They often show symptoms such as gingival enlargement, pain while chewing, and changes in appearance within 1 to 3 months of starting specific medications associated with the disease. The drug-induced gingival enlargement can create challenges in oral hygiene, leading to increased plaque accumulation and subsequent inflammation.[3]

Contrary to previous beliefs, not all drug-induced gingival overgrowth lesions are fibrotic. Histological analyses indicate that phenytoin-induced lesions are the most fibrotic, while cyclosporine-induced lesions are more inflamed with a lower fibrotic component, and nifedipine lesions exhibit a mixed presentation.[3]

Clinical features

Clinically, individuals with DIGO display firm, painless, nodular enlargement of the interdental papilla, mainly in the keratinized parts of the gingiva extending to the facial and lingual gingival margins. Severe cases may feature a significant fold of overgrown gingival tissue covering the crowns. In the absence of secondary inflammation, the tissue appears firm, pale pink, with small lobulations, protruding from under the gingival margin and is separated by a non-bleeding groove of tissue upon touch. If secondary inflammation is present, the gingiva looks smooth and red or bluish-red. The enlargement is typically generalized but more pronounced in the anterior regions. Typically, it is not observed in the edematous areas .[4]

ANTICONVULSANTS

Phenytoin (PHT; 5,5-diphenylhydantoin) was first introduced as an antiepileptic drug in 1938.

Since then, other anticonvulsant agents have been introduced that have

frequently been linked to clinically significant forms of gingival overgrowth. For example, gingival overgrowth cases after chronic use o gingivalenlargement f valproic acid, carbamazepine, or phenobarbitone in adult patients have been reported but are rare or have been poorly documented. In addition, valproic acid can affect the fetus also. A congenital case has been described in a child exposed to valproic acid in utero[(4)].

Mechanism of phenetoin-

Fibroblast from the phenetoin induced gingival outgrowth show increased synthesis of sulfated glycos aminoglycans in vitro .Phenetoin may induce a decrease in collagen-degradation as a
result of the production of an inactive fibroblastic collagenase

IMMUNOSUPPRESSANTS

Cyclosporine: potent immuno suppressive agent ,gingival enlargement caused by it is more vascularized than phenetoin enlargement. Effect children more frequently. The enlargement is due to the hypersensitivity reaction against cyclosporin as microscopic findings show many plasma cells and amorphous extracellular substance.Gingival enlargement is greater in patients who are medicated with both cyclosporin and calcium-channel blockers such as nifedipine. Another immunosuppressive drug ,tacrolimus,has been used effectively but it cause much less severe gingival overgrowth. (2)

CALCIUM CHANNEL BLOCKERS

Nifedipine,diltiazem,felodipine and verapamil are common calcium channel blockers. (2)(3)

Nifedipine induces gingival enlargement in 20% casesNifedipine also used with cyclosporin in kidney transplant patient and combined use of both cause large out growth.

1984 by Ramon et al. A case series was published reporting five similar cases of patients taking nifedipine regularly and who developed GO .Ramon et al. reported the presence of an inflammatory reaction in the nifedipine-induced hyperplasia, which suggests that rigorous hygienic measures might retard its progress and diminish its extent. Since then, many cases have been reported and published in the literature confirming Ramon's hypothesis on the association of nifedipine-induced gingival overgrowth (NIGO). Amlodipine-induced gingival overgrowth (AIGO) is less commonly reported and commonly present clinically several years after administering the drug. (2)(3)

CLASSIFICATION (5)

I. Inflammatory enlargement
   Acute
   Chronic
II. Drug induced enlargement

III. Enlargement associated with systemic diseases or conditions
IV. Neoplastic enlargement Benign tumors
   Malignant tumors
V. False enlargement

2. According to location and distribution, gingival enlargement:

Localized: limited to gingiva near to single or group of teeth .

Generalised : involving the gingiva throughout the mouth.

Marginal : near to gingival margin.

Papillary: near to interdental papilla

Diffuse: involving both marginal and attached gingiva along with papillae.

Discrete : pedunculated tumor like enlargement.

3. Scores of gingival enlargement are :

Grade 0: No gingival enlargement.

Grade 1: Enlargement associated to interdental papillae

Grade 2: Enlargement associated with papillae and marginal gingiva.

Grade 3: Enlargement covers ¾ of crown.

I.INFLAMMATORY ENLARGEMENT

- Acute
  i. Gingival abscess
  ii. Periodontal abscess
- Chronic

GINGIVAL ABSCESS

Definition : localized purulent infection that involves the marginal gingiva or interdental papilla.

found as acute inflammatory response to the forceful wedging of food or foreign body into the gingiva. Formerly, gingiva appears as erythematous swelling with smooth ,shiny surface. Within 24-48 hours ,the lesion usually becomes fluctuant from which pus may be expressed .

Etiology : Results from bacteria carried deep into the tissues when a foreign substance such as toothbrush bristle ,piece of apple core, lobster shell fragment is forcefully embedded into the gingiva . The lesion is confined to the gingiva and may be confused with lateral or periodontal abscesses .

Figure 1: Pre-operative extraoral photograph

Figure 2: Pre-operative intraoral photograph

Figure 3: Photograph showing the probing depth

PERIODONTAL ABSCESS

Definition: localized purulent inflammation in the periodontal tissue.

Also known as lateral abscess or a parietal abscess. Result in destruction of periodontal ligament and alveolar bone.

Signs and symptoms of periodontal abscesses

Acute

- Mild – severe discomfort
- Localized red ,ovoid swelling
- Periodontal pocket
- Mobility
- Tooth elevation
- Exudation
- Elevated temperature
- Regional lymphadenopathy

Chronic

- No pain or dull pain
- Localised inflammation
- Slight Tooth elevation
- Intermittent exudation
- Fistulous tract associated with deep pocket

Gingiva becomes soft and discolored due to edema and plaque induced cellular infiltration. It's common with scaling .Due to

surface dehydration causing irritation ,mouth breathers are commonly affected by gingivitis .

Inflammatory gingivitis may occur due to poor oral hygiene and improper endodontic treatment and use to orthodontic appliances causing gingival enlargement. (6)

I.Drug induced gingival enlargement

Drugs such as; **phenytoin,cyclosporine,and dihydropyrines** are mostly associated with gingival overgrowth. Phenytoin induced is the most common. In about 20-85% of individuals gingival enlargement may occur by an immunosuppressant namely .(6)

Drugs causing gingival overgrowth **(7)**

1. Convulsants

   Drugs ; PHT, valproic acid ,carbamazepine

   Therapy: treatment of epilepsy

   Incidences; 10- 83%

   Mechanism ; Blocking Na channels
2. Immunosuppressant's

   Drugs: CsA,TAC

   Therapy : Immunosuppression

   Incidence : 7- 80%

   Mechanism; Binding a protein in the cytosol.

3.Calcium channel blockers

Drugs: Amelodipine, nifedipin, felodipine, verapamil,dilitiazem. Therapy : Antihypertensive

Incidence : 30- 50 %

Mechanism: Blocking calcium channels .

Biochemical pathway hypothesis which included the following[9]:

1.increased connective tissue production following bacterial inflammation.

2. increased gingival fibroblast proliferation , connective tissue production following inducing drugs.

3. the biochemical reaction of the inducing drugs appear to have an inhibiting effect on cation channels.

4. cellular folate uptake is dependent upon both active transport through cation channels and passive diffusion

5. There is decreased folate uptake within gingival fibroblasts due to an inhibitory effect of the inducing drugs

6.Studys show that DIGO appears to be connected to an increased amount of connective tissue

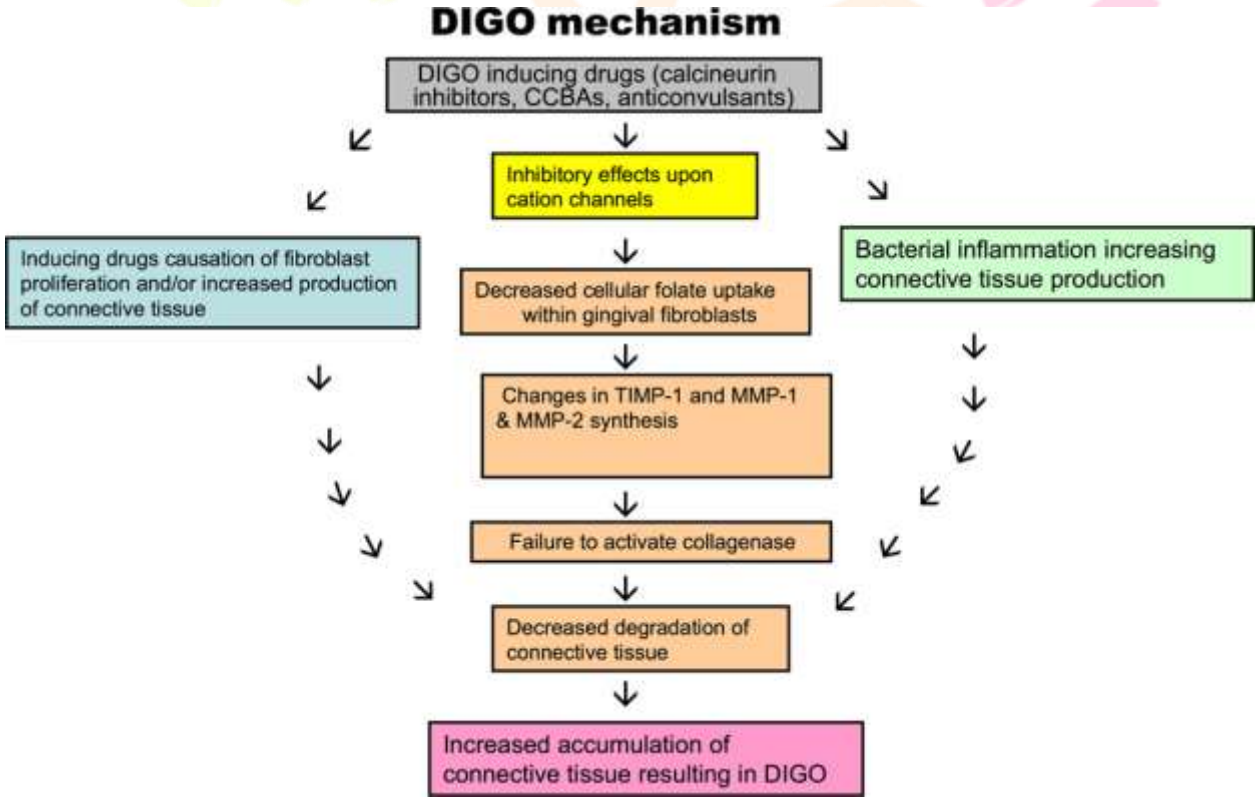
7. Research reveals that the activation of collagenase appears to be complicated and involves matrix metalloproteinase (MMPs)

8. Study's show that folate is necessary for amino acid and protein synthesis.

9. There is a chance that DIGO may be related to insufficient activation of collagenase necessary to degrade excess connective tissue

10.The possibility that DIGO may be secondary to insufficient degradation of excess connective tissue .

Mechanism of drug induced gingival overgrowth [7]

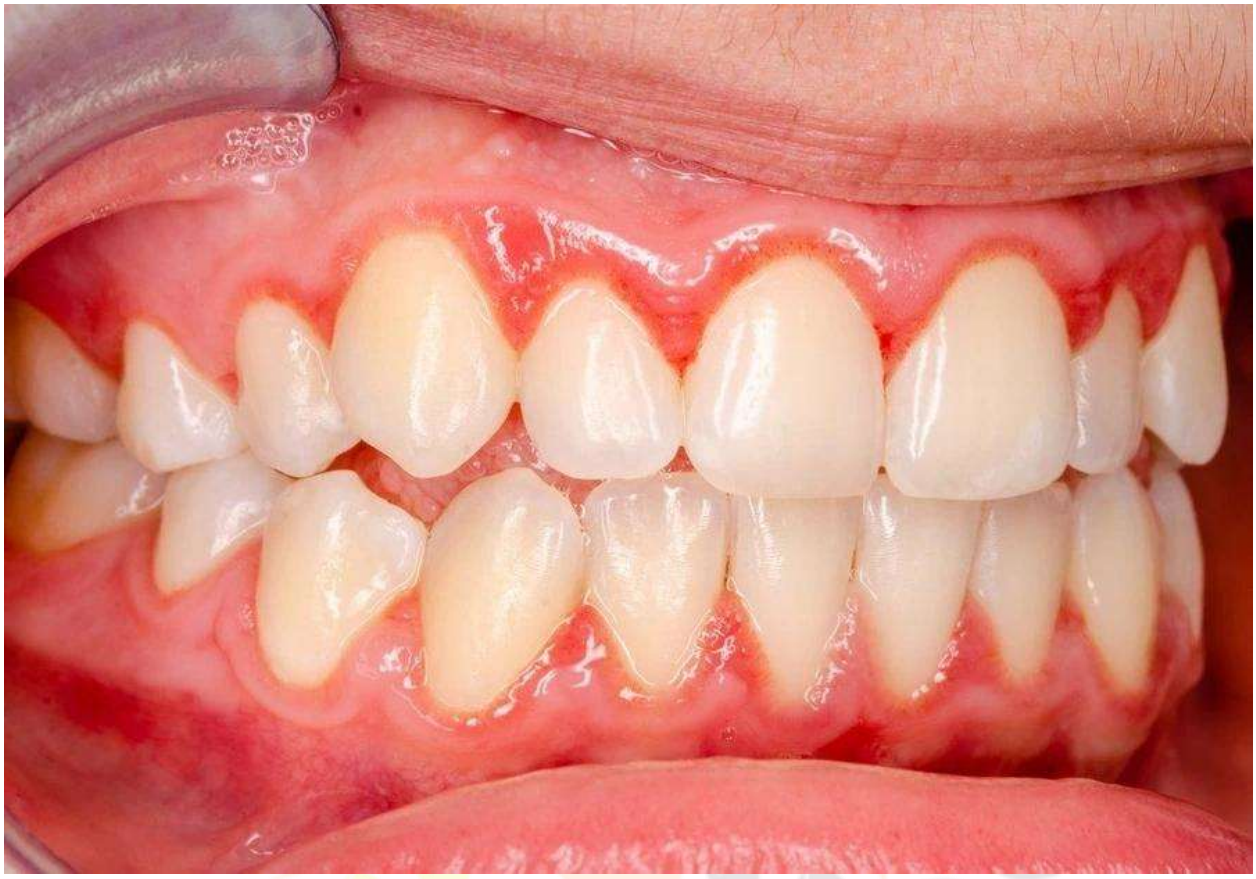


Calcium channel blockers such as nifedipine,felodipine and amilodipine,are also associated. Anticonvulsants like phenytoin ,phenobarbital,lamotrigine,valproate,vigabatrin,ethisuximide,topir amat e,and pyrimidine. (7)

I. Systemic factors related to gingival enlargement are

- *Pregnancy*

  Pregnancy gingival enlargement may be marginal and generalised or it may occur as a single mass or multiple tumor like masses .During pregnancy ,there is an increase in levels of both progesterone and estrogen which by the end of 3rd trimester reach level 10- 30 times the level during the menstrual cycle. These hormonal changes induce changes in vascular permeability, which leads to gingival edema and an increased inflammatory response to dental plaque . This includes an increase in *prevotella intermedia* .



Marginal enlargement

Observed as single enlargement referred as Pregnancy tumors .Pregnancy tumors are not neoplasm ; they represent inflammatory response to microbial plaque modified by patient condition. Appears usually after the third month. Incidence has been 10-70% .

Tumor like gingival enlargement

The so-called Pregnancy tumor is not a neoplasm ; it is an inflammatory response to bacterial plaque and it is modified by the patients condition. Usually appears after third month of Pregnancy but may occur earlier .incidence rate is 1.8- 5%

- *Puberty*

  Occurs in both male and female adolescents and appears in areas of plaque accumulation. Gingival enlargement nay vary in its size in contrast to the local factors . It is marginal and interdental is characterized by bulbous interdental papillae. Only the facial surface of gingiva or affected not the lingual surface. The mechanical action of tongue and excursion of food prevent the accumulation of local irritants heavily on the lingual surface. The distinguishing feature between Pubertal gingival overgrowth from the uncomplicated Chronic inflammatory gingival enlargement. After Puberty , the enlargement undergoes spontaneous decrease but doesn't disappear completely under the plaque and calculus are removed. Studies have shown that the hormonal changed coincide with an increase in the proportion of *Porphyromonas intermedia* and *Porphyromonas nigrescens.*

- Vitamin c deficiency

Included generally in scurvy. Acute vitamin c deficiency doesn't itself cause enlargement of gingiva but it may cause hemorrhage, collagen degeneration, and edema of gingival connective tissue .These changes modify the response of the gingiva to plaque to the extent that the normal defense delimiting reaction is inhibited and the extent of the inflammation is exaggerated ,thereby resulting in massive gingival enlargement seen in patients with scurvy. Gingival overgrowth with Vitamin c deficiency is bluish red ,soft ,and friable and has smooth ,shiny surface .Hemorrhage ,surface necrosis with pseudo membrane formation are common features .

- *Pyogenic granuloma*

Tumor like gingival overgrowth that is considered as an exaggerated conditioned response to minor trauma . It is similar to Pregnancy gingival enlargement clinically and microscopic.

Treatment consist of removal of the lesion plus the elimination of irritating local factors .The recurrence rate is about 15%.

Systemic diseases that cause gingival enlargement [8]

- *Leukaemia*

May be Diffuse or marginal and
Localised or generalised

.Appear as a Diffuse enlargement of the gingival mucosa ,an oversized extension of the marginal gingiva or a discrete tumor like interproximal mass. Clinically, patients with gingival enlargement is generally bluish red and shiny surface. The consistency is moderate to firm but decrease tendency towards friability and hemorrhage that occur spontaneously or with Slight irritation. Acute painful necrotising ulcerative inflammatory involvement may occur in the crevice formed at the junction of enlarged gingiva and the contiguous tooth surface .patients may have Chronic inflammation without the involvement of leukemic cells Observed clinically and microscopically .True enlargement occurs with acute/ subacute Leukemia .

Granulomatous diseases [8]

- *Wegener granulomatosis*

Rare disease characterized by acute granulomatosis necrotising lesion of the respiratory tract, including nasal and oral defects .acute necrotising vasculitis affects the blood vessels . The initially granulomatosis of the orofacial region include oral mucosal ulceration, gingival overgrowth, tooth Mobility, exfoliation of teeth and delayed healing response .The granulomatous papillary enlargement is reddish purple which bleeds easily .

- *Sarcoidosis*

Sarcoidosis is a granulomatous diseases of unknown etiology. Begins at the age of 20-30 years . Affected the blacks mainly and any organ

,including the gingiva ,in which a erythematous, smooth ,painless swelling seen .

II. Neoplastic Enlargement

- *Benign tumours of gingiva*

Epulis is a generic term used clinically to designate all discrete tumors and tumor like masses of the gingiva . Most lesions are inflammatory rather neoplastic.

In a survey the following were noted

Carcinoma 11.0%

Fibroma 9.3%

Giant cell tumors 8.4%

Papilloma 7.3%

Leukoplakia 4.9%

Angioma 2.5%

Osteofibroma 1.3%

Sarcoma 0.5%

Melanoma 0.5%c

Myxoma 0.45%

Fibropapilloma 0.4%

Adenoma 0.4%

Lipoma 0.3%

- *Fibroma*

Arise from the gingival connective tissue or from the periodontal ligament .slow growing spherical tumors. Can be firm and nodular but may be vascular and soft, Usually pedunculated.

- *Papilloma*

Papilloma are benign proliferation of surface epithelium, associated with human papilloma virus .Theyare solitary wart like or cauliflower like protuberance . They may be small and discrete or may be board ,Hard elevations with surface irregularity.

- *Peripheral Giant cell granuloma*

Arise interdentally from the gingival margin ,frequently on the labial surface , sessile pedunculated . Appearance varies from Smooth, regularly outlined masses to irregularly shaped,multilobulatwd protuberance ,With interdentations .The ulceration of the margin may be present. The lesions are painless, vary in size, and cover several teeth. Consistency may be spongy or firm .Color varies in pink to deep red or purplish blue .

The prefix *peripheral* is needed to differentiate them from comparable lesion that originate within the jawbone

Treatment and management

Treatment for Drug-Induced Gingival Overgrowth (DIGO) focuses on relieving discomfort, improving eating and chewing, reducing inflammation, swelling, and enhancing the cosmetic appearance

of the gingiva. Treatment options include medical and surgical approaches. Medical management is typically the initial choice, while surgery is considered for persistent cases or recurrences.

Considering discontinuation or changing the medication is crucial. For instance, alternatives to phenytoin like carbamazepine and valproic acid have shown lower rates of gingival enlargement. Diltiazem and verapamil are associated with a reduced prevalence of gingival enlargement compared to nifedipine. Substituting cyclosporin with tacrolimus,has or using azithromycin in combination with cyclosporin has demonstrated a decrease in DIGO severity.

Effective plaque control is essential, involving proper oral hygiene practices, professional plaque removal, tooth surface cleaning, and periodic scaling. Managing inflammation may include non-steroidal anti-inflammatory drugs, antibiotics for infection control, and topical antifungal medications such as nystatin. Folate supplementation has also been utilized in treatment protocols.After discontinuing the causative drug, it is recommended to allow a sufficient period of 6 to 12 months to elapse to observe improvements in the condition[9, 10,11.12,)]

Conclusion

Drug induced gingival enlargement is one of the mostly seen gingival enlargement induced bt systemic medications.

Hence it would be more useful if we understand the possible risk factors involved.The pathogenesis is complex and still incomplete.Phenytoin,Cyclosporine A and Nifedipine are the main drugs which induce gingival enlargement. Our data suggest that initial periodontal therapy and replacing drugs may be useful for treating patients with heavy periodontitis and relatively mild gingival enlargement.For those patients who cannot replace medications, basic periodontal treatment, Periodontal surgery, and timely and effective periodontal maintenance therapy can also be used to treat and prevent recurrence.

References

- Ref 1; Marshall RI, Bartold PM. Medication induced gingival overgrowth. *Oral Dis.* 1998;4:130–51. [PubMed] [Google Scholar]
- Ref 2; Dongari-Baqtzoglou A. Research, Science and therapy committee, american academy of periodontology. Drug-associated gingival enlargement. *J Periodontol.* 2004;75:1424–31. [PubMed] [Google Scholar]
- Ref 3;Dongari A, McDonnell HT, Langlais RP. Drug-induced gingival overgrowth. Oral Surg Oral Med Oral Pathol. 1993 Oct;76(4):543-8. [PubMed]
- Ref 4; Trackman PC, Kantarci A. Molecular and clinical aspects of drug-induced gingival overgrowth. J Dent Res. 2015 Apr;94(4):540-6. [PMC free article] [PubMed]
- Ref 5;Marshall RI, Bart old PM. A clinical review of drug-induced gingival overgrowths. Aust Dent J. 1999;44:219–32. [PubMed] [Google Scholar
- Ref6;. Rodríguez-Vázquez M, Carrascosa-Romero MC, Pardal-Fernández JM, Iniesta I. Congential gingival hyperplasia in a neonate with foetal valproate syndrome. Neuropediatrics. 2007;38:251–2. [PubMed] [Google Scholar]

- Ref 7;E.Hyperplasia gingivae diphenylhydantoinea,Oslo,1963, Universitetsforlaget.

- Ref 8;Hallmon WW,Rossmann JA: the role of drugs in the pathogenesis of gingival overgrowth

- Ref 9;Mavrogiannis M, Ellis JS, Thomason JM, Seymour RA. The management of drug-induced gingival overgrowth. J Clin Periodontol. 2006 Jun;33(6):434-9. [PubMed]

- Ref 10; Dhale RP, Phadnaik MB. Conservative management of amlodipine influenced gingival enlargement. J Indian Soc Periodontol. 2009 Jan;13(1):41-3. [PMC free article] [PubMed]

- Ref 11;Lu HK, Tseng CC, Lee YH, Li CL, Wang LF. Flutamide inhibits nifedipine- and interleukin-1 beta-induced collagen overproduction in gingival fibroblasts. J Periodontal Res. 2010 Aug;45(4):451-7. [PubMed]

- Ref 12 ;Kim JY, Park SH, Cho KS, Kim HJ, Lee CK, Park KK, Choi SH, Chung WY. Mechanism of azithromycin treatment on gingival overgrowth. J Dent Res. 2008 Nov;87(11):1075-9. [PubMed