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Drug-induced gingival enlargement – Oral implications for prescribing physicians

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ABSTRACT

A male patient presented with a main complaint of persistent growth of the upper and lower gingiva that bled easily and resulted in an inability of maintaining proper oral hygiene. He reports that the growth of the gingiva started approximately three years prior to consultation in our clinic and is asymptomatic. His medical history revealed that he suffers from epilepsy and was being treated with a daily anticonvulsant, namely Phenytoin (100mg).

Full-mouth non-surgical periodontal therapy was performed and supplemented with an adjunctive chlorhexidine mouth rinse as a chemical plaque control mechanism. Part of the systemic phase of management of the patient, involved requesting the medical physician change the current epilepsy medication to Epilim®, which was beneficial in contributing to the resolution of gingival enlargement. Significant reduction in gingival inflammation and enlargement were achieved with the non-surgical treatment. Corrective surgery therapy was performed to treat those areas of DIGE that had not resolved.

Acronyms

DIGE - Drug-induced gingival enlargement
GH – Gingival hyperplasia

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Key Words

gingival enlargement, drug-induced gingival enlargement, gingivitis

BACKGROUND

The Department of Oral Medicine and Periodontics (Faculty of Dentistry, University of the Western Cape) has in the recent years experienced an increase in the number of patients presenting with gross enlargement of the gingiva due to the prescription of medications for a variety of systemic conditions. A significant increase in the number of gingival enlargement cases has been observed in patients taking Phenytoin® presenting to the Faculty of Dentistry (UWC) for management. There could be a variety of reasons for this increase, which one include an increased awareness of oral lesions by the patients or that medical personnel have adopted a protocol of considering oral health management as a part of holistic patient care. It is thus imperative that prescribing practitioners are aware of the potential adverse effects of certain medications on the gingiva and overall oral health of the patient.

CASE PRESENTATION AND MANAGEMENT

A 32-year-old male presented at the Oral Medicine Clinic at the University of the Western Cape Dental Faculty (UWC), Tygerberg campus. His main complaint was an approximate three-year history of painless, persistent growth of the upper and lower gingiva in both jaws, that bled easily and resulted in him not being able to brush his teeth adequately.

His medical history evaluation revealed that he suffers from epilepsy, and he was being treated with anticonvulsant (Phenytoin 100mg daily).

Extra-oral examination of the head and neck region revealed bilateral palpable submandibular lymphadenopathy. The intra-oral examination demonstrated diffuse, gross enlargement of the gingiva on both the mandible and the maxilla. The gingiva was inflamed and demonstrated a tendency for spontaneous bleeding. Gross plaque and calculus deposits presented on all teeth throughout the oral cavity. (Figure 1 & 2)

MANAGEMENT

The gross enlargement of the gingival tissues promotes poor

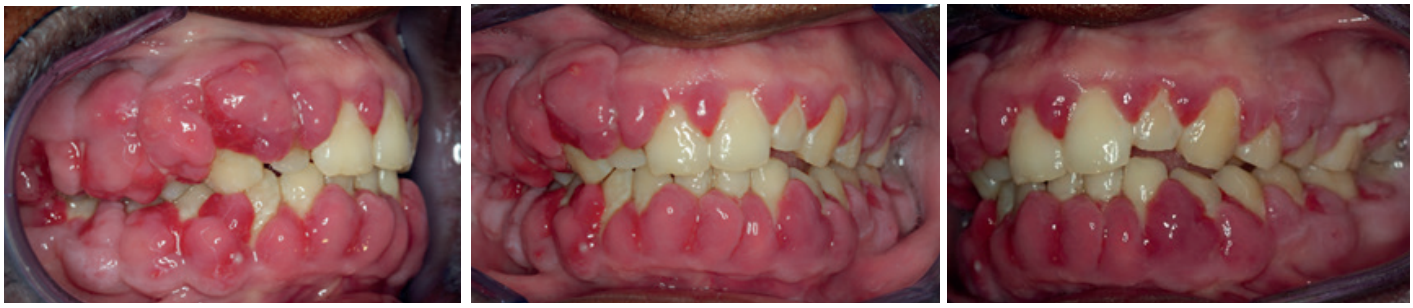

Figure 1: Shows labial and buccal aspect with gross hyperplastic gingival tissue and plaque deposits associated with poor oral hygiene maintenance.

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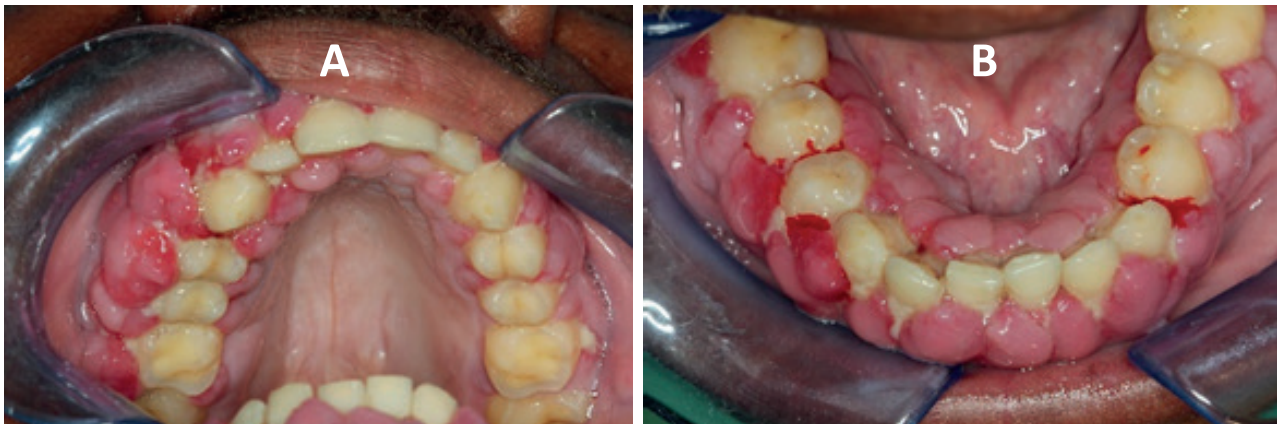

Figure 2: Shows the hyperplastic gingival tissue involving the palatal and lingual aspects of the maxilla and mandible.

oral hygiene as the patient is unable to adequately brush the teeth. Therefore, the biofilm remains undisturbed, and inflammation persists leading to more hyperplastic response of the gingiva and even the progression of periodontal disease. Removing plaque disturbs the biofilm and resolves inflammation.

The management of this patients was structured into the following phases:

Systemic Phase

Consultation with the physician was arranged and it was decided to discontinue phenytoin and replace it with Epilem™ which resulted in similar management of epilepsy but with more manageable oral adverse side effects.

Initial Phase

A comprehensive oral hygiene education was provided to institute adequate homecare maintenance by the patient. Full mouth non-surgical periodontal therapy was performed, and the patient was provided a 0,2% chlorhexidine based mouth rinse as an adjunctive chemical plaque control measure.

Due to the amount of gross calculus and plaque deposits on the teeth, a two-week follow-up interval was performed to enforce the oral hygiene and evaluate progress of the initial phase of treatment (Figure 3 & 4). The professional removal of plaque reduces the level of inflammation and allows for a resolution of the gingival enlargement to a certain degree. The benefit of reducing gingival inflammation is it assists in reduction of the gingival enlargement, and it reduces the level of bleeding tendencies during surgical interventions if treatment proceeds into the surgical corrective phase.

Significant reduction in the degree of gingival hyperplasia was present. However, it was decided that the patient would benefit from another session of non-surgical periodontal therapy to further reduce the levels of plaque accumulation and ultimately reduce the extent of the gingival inflammation still present.

At this stage another 2 week follow-up consultation was made to monitor the progress and further enforce the oral hygiene practices of the patient. (Figure 5 & 6)

Corrective Phase

Once there was resolution of the gingival inflammation and significant reduction in the gingival enlargement, it was decided to proceed with a gingivectomy to correct the contours of the gingiva on areas that showed incomplete resolution was performed. (Figure 7)

The sites considered included the anterior labial aspect of the mandible and the buccal aspect of the first quadrant. (Figure 7) Surgery was done using the gingivectomy knives by placing a partial thickness incision on the keratinised mucosa affected. The incision run from the distal central incisor of the first quadrant to the mesial second molar in the maxilla and between the mesial aspects of the first premolars in the mandible. A second salcular incision is made parallel to the initial incision then joined. The affected tissue is than removed following partial thickness flap elevation leaving behind exposed connective tissue. No dressing is placed, and the site is set to heal by secondary intention.
The post-operative medication involves the use of 0.2% chlorhexidine mouth wash and analgesics including paracetamol and non-steroid anti-inflammatory drugs to minimise swelling and discomfort.

The two weeks follow up following the gingivectomy procedure showed good post-operative results with healed gingiva and a greatly improved oral hygiene status. (Figure 8)

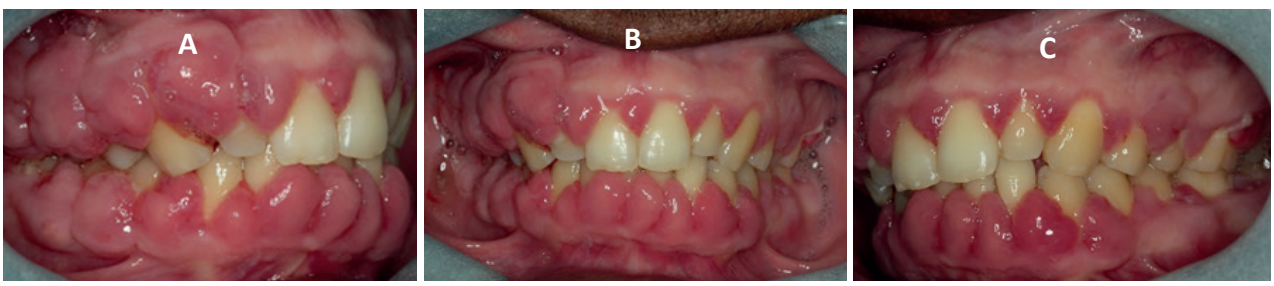

Figure 3: Shows hyperplastic tissue on the buccal and labial aspect 2 weeks after initial phase treatment. Notice the reduction in the extent of the erythema of the gingiva (3.B).

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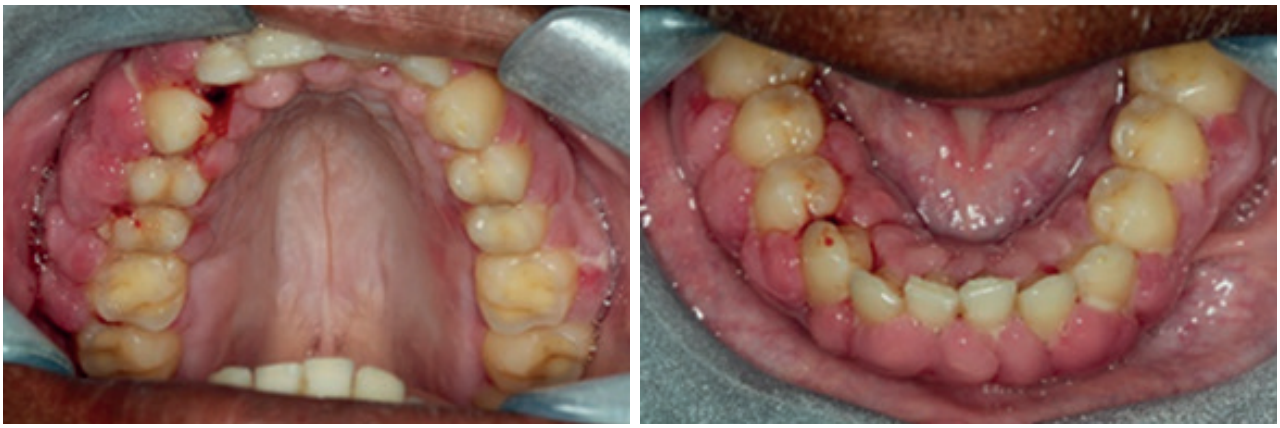

Figure 4: Shows hyperplastic tissue on the palatal and lingual aspect 2 weeks after initial phase treatment.

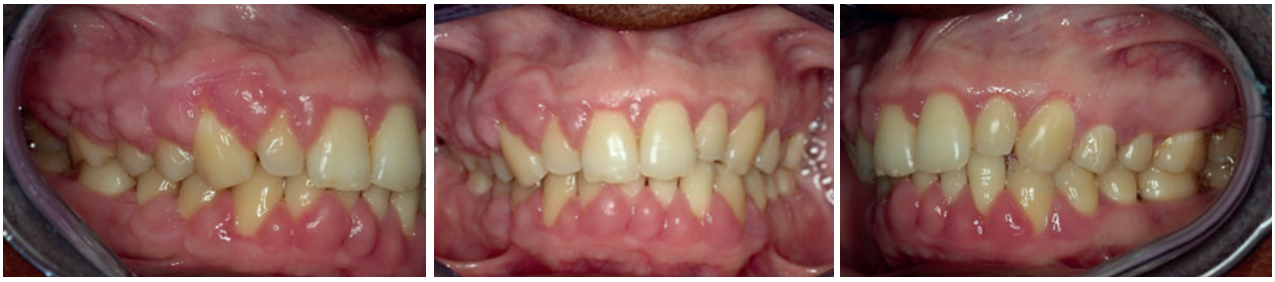

Figure 5: Shows extensive improvement in the appearance of the gingival tissues. Some hyperplastic gingival tissue still noted on the anterior labial aspect and the first quadrant. Note the improvement of the oral hygiene and absence of erythema.

Maintenance Phase

Following a complete resolution of the gingival enlargement, the patient was given a three months follow-up consultation for maintenance and thereafter, routine six monthly dental consultations. During the 6 monthly visits non-surgical periodontal therapy is performed together with continued enforcement of adequate oral hygiene education.

DISCUSSION

There are many factors attributing to the development of gingival enlargement, which can present either as localised or generalised. Alteration of the gingival tissues dimensions is considered a consequence of a pathologic event. However, most enlargements of the gingiva can be reversible, while some cases following a chronic pathway may advocate surgical interventions.[1]

Pathology of the gingiva, as in all other pathologic processes, may results in three clinical outcomes following inflammation of the periodontium. The clinical gingival lesions may either (1) undergo complete resolution of the inflammation and the tissues regain a state of health (i.e., homeostasis), (2) progress to destruction of the periodontal tissues leading to evident loss of clinical attachment and ultimately loss of dentition (i.e., periodontitis), (3) or the body responds by tissue fibrosis.[1]

Tissue fibrosis develops as a defence mechanism attempting to prevent progression of inflammation. Within the gingival connective tissue fibroblasts lay down an increased amount of collagen and non-collagenous proteins. This increased deposition of the matrix is not adequately balanced by degradation of the matrix composition by the lytic enzymes, resulting in a clinically visible fibrotic changes of the gingiva. (As seen in Figure 1 & 2). This clinically apparent gingival hyperplasia by fibrosis is commonly referred to as gingival enlargement and these lesions are unique in their pathogenic mechanisms.[2]

Drug-induced gingival enlargement (DIGE) is the most studied cause of these lesions with anticonvulsant medication being highly implicated. There are a variety of

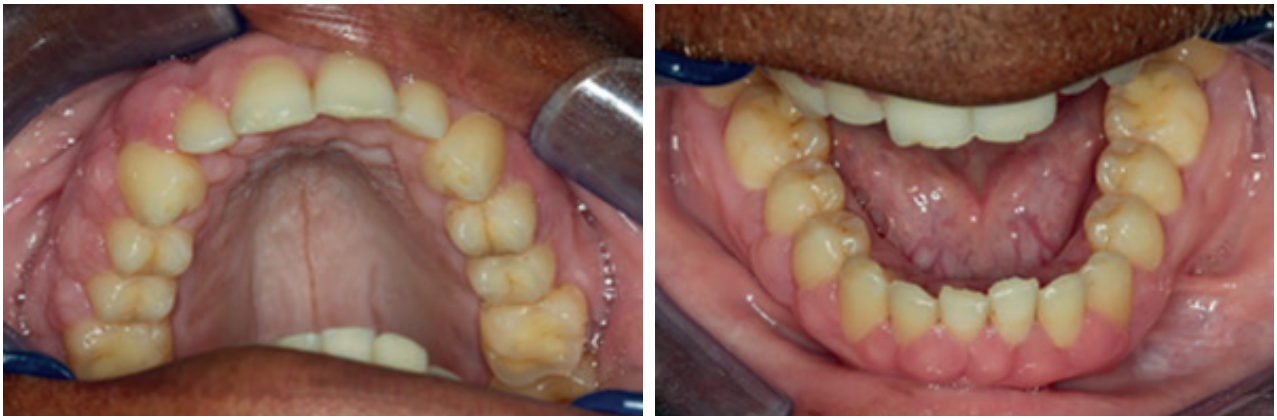

Figure 6: Shows gingival tissue improvement on the lingual and palatal aspects.

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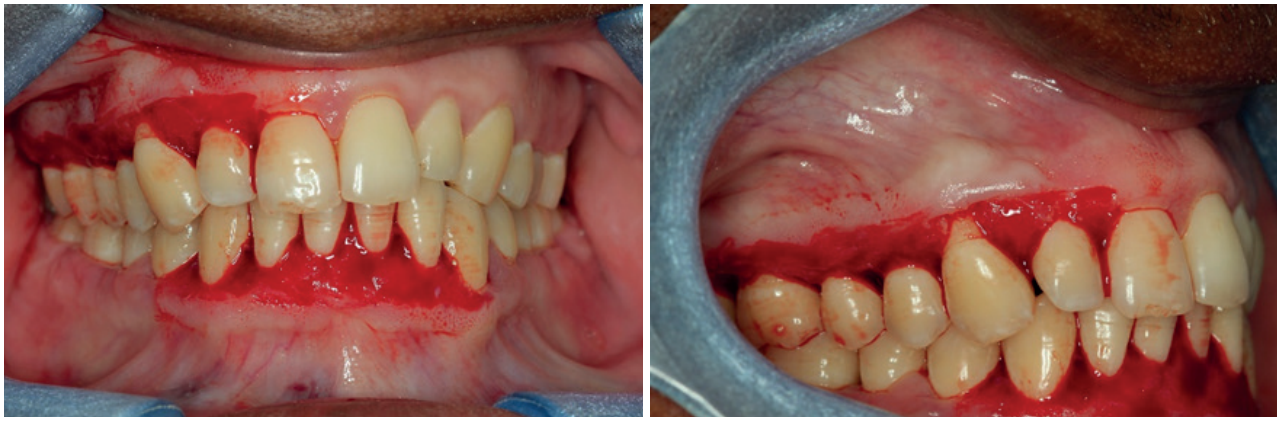

Figure 7: Gingivectomy was performed to eliminate excess gingival tissue. An external bevel incision was performed since there is keratinized mucosa of more than 5mm. Note the gingival recession on the 13 area, which was not considered for treatment at this particular stage, however possible procedures for recession coverage were discussed with the patient.

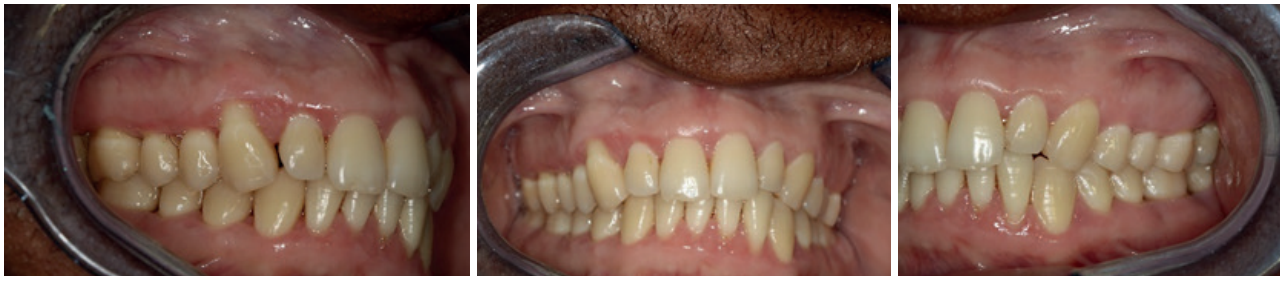

Figure 8: Shows a completed treatment of the gingival hyperplasia as a main complaint. The gingival recession was left untreated upon request by the patient.

reasons a patient may present with gingival enlargement; this article focuses on only the drug-induced variants with emphasis on phenytoin. [2]

4.1 Aetiology and Classification of Gingival Enlargement

Gingival enlargement cases can be classified according to the associated aetiologies as follows: Inflammatory enlargement following an acute or chronic case of gingivitis, drug-induced gingival enlargement (DIGE), gingival enlargement associated with systemic conditions, gingival enlargement associated with neoplasms and false enlargement.[3] Although not discussed further here, it should be noted that gingival enlargement may also be associated with life-threatening systemic diseases such as leukemia and thus a comprehensive examination to reach a diagnosis is of great importance.[2, 3]

Three drug groups have been identified as to be commonly associated with DIGE namely: antihypertensives (calcium channel blockers), anticonvulsants and immunosuppressants. DIGE will be the focus of this article.

Table 1: Numerous aetiologies of gingival enlargement have been identified.

Aetiologies and classification of gingival enlargement	
1.	Inflammatory enlargement
	A. Chronic Acute
2.	Drug induced gingival enlargement (DIGE)
3.	Enlargement associated with systemic disease or conditions
	A. Conditioned enlargement
	• Pregnancy
	• Puberty
	• Vitamin C deficiency
	• Plasma cell gingivitis
	• Non-specific conditioned enlargement (e.g., pyogenic granuloma)
B.	Systemic diseases causing gingival enlargement
	• Leukemia
	• Granulomatous disease (e.g. Wegener's granulomatosis, Sarcoidosis)
4.	Neoplastic enlargement
	A. Benign
	B. Malignant
5.	False enlargement

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4.2 DIAGNOSIS

Since it has been established that gingival enlargement is usually associated with systemic conditions, including medical physician's input on the overall examination becomes very important in reaching a correct diagnosis and ultimately adequately addressing the presenting main complaint.[3]

Reaching an accurate diagnosis requires a comprehensive review of the presenting medical history and a precise clinical presentation must be categorised in either a localised or generalised distribution of the lesions. The localized form may only be confined to papillae or involve thirty percent or less of the entire gingival tissue while the generalised gingival hyperplasia involves usually the entire gingival tissue. Clinically the affected gingiva develops a thickened, lobulated appearance. The gingival enlargement can progress to eventually completely cover the anatomic crowns of teeth. Associated symptoms may include pain, tenderness, bleeding and discomfort during mastication.[4]

During a dental examination the degree of gingival enlargement can be scored according to table 2 below:[2]

Table 2

Gingival Enlargement Clinical Scoring	
Grade	Description
Grade I	No signs of gingival enlargement
Grade II	Enlargement confined to interdental papilla
Grade III	Enlargement involves papilla and marginal gingiva
Grade IV	Enlargement covers three-fourths or more of the crown (Figure 1)

4.3 DRUG-INDUCED GINGIVAL ENLARGEMENT (DIGE)

The most implicated drugs in development of gingival enlargement are used in treatment of serious disease including antihypertensives, anticonvulsants and immunosuppressants. Three drugs associated with gingival enlargement (mentioning the most encountered during a dental consultation) are nifedipine, phenytoin and cyclosporine.[3]

DIGE generally presents 3-6 months after the onset of the use of these medications.[4] It should be noted that not all patients being treated with these drugs will ultimately develop hyperplastic enlargement of the gingival tissues in the oral cavity.[1,2] A common observation in the development of DIGE is that the event is secondary to poor general hygiene of the oral cavity resulting in the accumulation of an undisturbed biofilm and ultimately inflammation of the gingiva.[3] The host responds by fibrosis of the gingival tissues. The degree of inflammation and fibrosis is heavily dependent on the type of drug used, dosage, and duration of drug use and oral hygiene status of the patient. It may also depend on the individual susceptibility including genetic factors together with environmental factors.[3]

4.3.1 Anticonvulsants

Phenytoin (diphenylhydantoinate) is an anti-epileptic drug, also called an anticonvulsant. It works by slowing down impulses in the brain that cause seizures. In South Africa it is a drug of choice in the treatment of grand mal, psychomotor and temporal lobe seizures. The estimated prevalence of this type of DIGE is about fifty percent of the global population.[4]

The onset of gingival enlargement is observed as early as one month after the onset of drug prescription. The increase in the lesion severity progresses with the increased duration of drug use. The buccal gingiva of both the maxilla and the mandible are the commonly affected sites, but an involvement of the entire dentition may be observed in severe cases (Figure 1).[4,5]

Major characteristics of these type of DIGE are the increase in tissue volume of the interdental papillae and thickness of the marginal gingiva resulting in the functional and aesthetic concerns.[6]

4.3.2 Antihypertensives (calcium channel blockers)

This group of drugs are mainly used to treat hypertension, coronary artery disease, angina pectoris and cardiac arrhythmia.[19] Phenylalkylamine derivatives (e.g., verapamil), Benzothiazepine derivatives (e.g., diltiazem), and dyhydropyridines (e.g., amlopidine, nifedipine, nisoldipine) are different types of drugs implicated in the development of gingival hyperplasia.[7,8]

4.3.3 Immunosuppressants

Immunosuppressants are widely used for the prevention of solid organ and bone marrow transplants and for the treatment of autoimmune disorders. Cyclosporin A is a widely used agent in most of the cases.[9] These lesions are characteristically limited to the buccal aspect of both the maxilla and the mandible. The severity may be just as like that of phenytoin.[3,9]

4.4 PATHOGENESIS OF DRUG-INDUCED GINGIVAL ENLARGEMENT

The mechanisms leading to DIGE is mediated through defective functioning of the fibroblast in the gingival tissues. The implicated medications directly affect the metabolism of the extracellular matrix by reducing enzymatic activity of collagenase while elevating the production of matrix proteins.[3]

Over and above the effects imposed by these drugs on the fibroblast, the host inflammatory regulation of tissue turnover becomes the major factor in the pathogenesis of gingival enlargement.[6]

Studies evaluating tissues from gingivectomy procedures have demonstrated some differences in the cellular and molecular features in the tissues depending on the type of drug the patient was prescribed.[6] Gingival enlargements associated with phenytoin demonstrates more fibrosis;

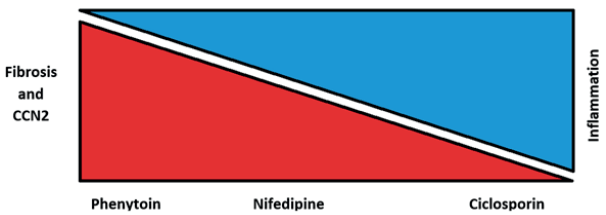

Figure 9: Relationship between inflammation, fibrosis and medications associated with gingival enlargement. The left side demonstrated high levels of fibrosis accompanied by high expression of CCN2 (also known as connective tissue growth factor – CTGF). The right side represents high inflammation and lower levels of fibrosis.[21]

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cyclosporin affected tissues present with more inflammation and less fibrosis, while nifedipine induced enlargement are mixed.[6]

Hassell et al, in 1991 suggested that in phenytoin-induced gingival enlargement the fibroblasts are characterised by the increased synthesis of the collagen. They further deduced that gingival fibroblast from nifedipine-induced gingival hyperplasia have defective production of collagen resulting from reduced collagenasese activity also resulting in deposition of collagen.[9]

Tipton *et al,.* in 1994 concluded that calcium channel blockers decrease calcium levels in gingival fibroblast and T cells though the process of interfering with the metabolism of calcium. This results in interference in the T-cell proliferation and/or activation and biosynthesis of collagen.[10]

Cyclosporin appears to promote inflammation and tissues fibrosis by initiating an exaggerated innate immune response and has anti-fibrotic effects on collagen biosynthethesis and deposition.[21] Cyclosporin targets cyclophilin, subsequently disrupting collagen deposition and maturation in part by inhibition of prolyl-3-hydroxylase activity.[21]

The functions of fibroblasts such as proliferation, differentiation and synthesis of extracellular matrix are regulated or controlled by levels of host cytokines and growth factors.[5, 9, 10, 19] Molecular studies on tissues with drug-induced gingival enlargement are typically characterised with elevated levels of platelet-derived growth factors (PDGF), interleukin-6, interleukin-1β, transforming growth factor-β (TGF-β), fibroblast growth factor 2 (FGF2) and connective tissue growth factor (CTGF).[11, 16] Macrophages are the main source of these cytokines and the TGF-β1-CTGF pathway has well been noted as an essential mechanism resulting in the formation of gingival enlargement.[12]

TGF-β is found in high concentrations in platelets, macrophages, neutrophils and fibroblasts. TGF-β acts mainly on fibroblasts and endothelial cells and results in collagen and matrix synthesis.[15]

CTGF (also known as CCN2) is a reliable marker of fibrosis and contributes to development of fibrosis initiated by TGF-β. 15 CTGF is synthesized by endothelial cells and fibroblasts and has mitogenic and angiogenic functions. CTGF acts as autocrine growth factor in response to TGF-β. 15 Cellular proliferation and differentiation in the gingival tissues is regulated by TGF-β1 and may activate gene expression for the synthesis of extracellular matrix components.[13, 17] TGF-β1 induces connective tissue growth factor mRNA and protein expression in human gingival fibroblasts. The TGF-β1–CTGF pathway directly regulates fibrosis, gingival fibroblast lysyl oxidase, and collagen generation. CTGF expression is increased in all forms of gingival enlargement, with the highest levels occurring in phenytoin-induced gingival overgrowth.[13, 18]

The expression of the CTGF is not only limited to the connective tissue but also demonstrated in the gingival epithelium in abundance around the basal epithelial cells.[14] Black SA et al, 2007 revealed a unique mechanism for TGF-β1- induced CTGF expression in fibroblast regulated by prostaglandin E2, mitogen-activated protein kinases (MAPKs) Camp and activation of Jun N-terminal Kinases (JNKs).[15]

This is a key event in the pathogenesis of DIGE in some degree of epithelial-mesenchymal transition induced by medication.[3, 6, 8, 15] Elevated levels of fibrosis on soft tissues is characterised by the elevated epithelial-mesenchymal transition, through which fibroblast function is acquired by epithelial cells in the gingiva, the process is regulated by CTGF. [14]

Phenytoin has also been found to suppress extracellular matrix-degradation by inhibition of lysosomal enzymes (cathepsin I, matrix-metalloproteinase-1, tissue inhibitor of matrix metalloproteinase-1). Through this mechanism there is suppression of extracellular matrix and collagen degradation.[21]

Phenytoin may also cause a decrease in sodium and calcium flux, as well as a reduction in cellular folic acid uptake. This subsequently results in a localized folate deficiency in the gingival tissue – which can cause degenerative changes in the sulcular epithelium and may also exacerbate inflammation. [21]

4.5 MANAGEMENT

Gingival enlargement causes significant difficulties for patients to maintain their oral hygiene. This gross enlargement of the gingiva can also results in difficulties with mastication, poor aesthetics and can negatively impact the patients quality of life and overall health.[22] The presence of gingival inflammation associated with poor oral hygiene and plaque accumulation, serves as a major risk factor to the onset and worsening of DIGE. [20, 21]

Non-surgical periodontal therapy has reported to be able to reduce the size of the clinical lesions by up to 40%, due to the removal of bacteria and the resultant reduction in tissue inflammation.[22] In most cases (approximately 60 %) the fibrotic gingival enlargement requires surgical intervention. Studies have reported that up to 34% of cases can present with recurrence after 18 months following non-surgical and surgical periodontal therapy. [23] Some studies have reported that alternative surgical interventions (such as the use of a laser excision) can result in reduced recurrences compared with conventional gingivectomy techniques.[23] Long-term maintenance and follow-up of these patients remains essential due to the continuous use of the associated drugs.[22] It has been demonstrated that if a patient is placed on a preventative dental program and effective oral hygiene is maintained, the occurrence of DIGE can be minimised.[23]

Some animal studies have been conducted evaluating the potential use of statins in preventing phenytoin-induced gingival enlargement.[32] This is based on the findings that statins inhibit HMGCoA reductase, which is required for the biosynthesis of mevalonate-derived active geranylgeranylated RHO family small G-proteins, including RAC1, CDC42 and RHOA. Active RAC1 and CDC42 are uniquely required for TGF-β stimulated CCN2 (CTGF) levels in gingival fibroblasts.[19]

4.6 RECOMMENDATIONS

DIGE is an adverse effect of drugs used to treat serious systemic conditions that may at times be life threatening, it would be a good clinical practice that medical and dental

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teams work together to maintain patients who take the implicated drugs.[20]

Patients taking these medications should be adequately educated on the potential adverse effects on the oral cavity. The patients at risk for DIGE need to be monitored frequently with a thorough full-mouth debridement to reduce any inflammation of the gingival tissues and be placed on a strict homecare oral hygiene regimen.

5. TEACHING POINTS

- When prescribing drugs that can potentially induce gingival hyperplasia, involvement of oral and dental care is advocated
- Good oral hygiene habits may prevent secondary induction of drug-induced gingival hyperplasia

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