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Gingival Hyperplasia - A Multifaceted Enigma

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ABSTRACT
Gingival hyperplasia or, gingival enlargement has become an increasing concern due to a number of factors prevalence whether it be an inflammatory enlargement or a drug induced enlargement; hyperplasia associated with conditions like pregnancy, puberty, vitamin C deficiency or systemic diseases like leukaemia, sarcoidosis and Wegener granulomatosis; whether it be a neoplasm addressed as "gingival tumours" or a false gingival hyperplasia. All these entities and conditions seriously impose a massive effect on the gingival tissue. Drug induced gingival overgrowth occurs due to adverse effects of drug reactions or adverse drug reaction (ADR), it occurs specifically in patients who are under the influence of immunosuppressives, calcium channel blockers, anticonvulsants, cyclosporine, phenytoin, etc. As the growth of the gingiva occurs patient complains of pain which affects many other functions like masticatory functions and also disfigures the condition of the gingiva. Among many people it is a cause of concern and other unwanted effects. Here we discuss a case that demonstrates the effect of amlodipine on gingival tissues.[3]

Keywords: *gingival hyperplasia, epulis, gingival disease, gingival overgrowth, calcium channel blockers, amlodipine*

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I. INTRODUCTION

Gingival hyperplasia or overgrowth or may also be known as inflammation are frequent features of gingival disease. They are generally characterized by increase in size. They can be isolated, regional or generalized.[1] They can be again categorized by etiopathogenesis, location, size, extent. Based on etiopathogenesis - Inflammatory, drug induced, neoplastic, false enlargement, systemic condition. Based on location – **Marginal, papillary, and diffuse**. Based on distribution – Localized (isolated, discrete, regional), localized enlargement of the gingiva may also be called as epulis. Generalized enlargement is present in more than one area of the gingiva.[2]

Gingival enlargement from inflammatory conditions may either be acute or chronic, chronic being commonest cause. This is represented as a ballooning enlargement of the interdental papillary tissue and marginal gingiva. Sometimes, this is also presented as a sessile or pedunculated growth on the gingival tissue resembling a tumour and thus giving a differential diagnosis of pyogenic granuloma or a fibroma. The main cause of this type

of enlargement is long term exposure to dental plaque. On the other hand acute inflammatory enlargement can be due to gingival abscess.[3]

Conditioned gingival enlargement can be due to physiological hormonal conditions such as pregnancy and puberty, some nutritional causes such as vitamin C deficiency presenting as a classic condition of scurvy showing haemorrhage, collagen degeneration and gingival oedema. Some non – specific gingival enlargement include pyogenic granuloma, sometimes referred to as "pregnancy tumour".[4] Some systemic causes include leukaemia which may present as diffuse or marginal, localized or generalized.

Gingival enlargement may also be due to a neoplastic cause such as some benign tumours like epulis, fibroma, papilloma, peripheral giant cell granuloma, central giant cell granuloma, leukoplakia, gingival cyst, myoblastoma, nevus, haemangioma, mucoceles, ameloblastoma.[5] As well as some malignant causes like carcinoma and malignant melanoma showing a vertical growth phase.

False gingival enlargement has also become very prevalent being due to an underlying osseous condition of osteoma or osteosarcoma or an underlying dental condition of tooth developmental enlargement later discussed.

An important increasing concern of gingival hyperplasia are drug induced enlargement such as due to long term intake of anticonvulsants like **phenytoin** (Dilantin), **ethotoin** (Peganone), **mephenytoin** (Mesantoin), **ethosuximide** (Zarontin), **methsuximide** (Celontin), **valproic acid** (Depakene).[6,12] Some Immunosuppressants induced gingival enlargement due to **cyclosporine**. Some calcium channel blockers which induce gingival hyperplasia include dihydropyridine derivatives like **amlodipine** (Lotrel and Norvasc), **felodipine** (Plendil), **nicardipine** (Cardene), **nifedipine** (Procardia); **benzothiazine** derivatives and **phenylalkylamine** derivatives.[12,13]

Hence we discuss the cause of gingival growth which is a very common clinical finding. The cause of this case is bit different.

We discuss this case because it initially looked like a much more dangerous malignant lesion, but upon investigation it revealed that it was a rather harmless benign gingival enlargement. That being said it was still a challenging case due to its varying cause.

II. CASE REPORT

A 60-year-old male patient reported to the Department of Oral and Maxillofacial Pathology at Kusum Devi Sunderlal Dugar Jain Dental College and Hospital, Kolkata, India, with a chief complaint of swelling in the gums of left and right back tooth region since 2 months that gradually increased in size. The patient's medical history revealed that he was hypertensive for last 20 years and was receiving a single dose of amlodipine 5 mg/day orally for the past 8 years.

Patient gave a history of smoking 40 cigarettes daily for the past 20 years and khaini use 10 times daily for the last 30 years.

Intraoral examination revealed generalized pink gingiva with rolled gingival margins, lobulated papillae, and fibrous overgrowth throughout the maxilla and mandible, particularly on the labial and buccal side (Figure 1). A prominent nodular growth was also seen on the palatal aspect of the maxillary molars, which was approximately 5.0 cm x 3.0 cm in at greatest diameter, non-pulsatile, tender, firm on palpation (Figure 1). Swelling was erythematous, oedematous with slight spring-back of tissue. Generalized deep pockets, exudation on application of digital pressure, and bleeding on probing were noted. The oral hygiene status of the patient was poor, accompanied by plaque and calculus accumulation around all teeth. Clinically, the differential diagnosis for the localized growth included pyogenic granuloma, fibroma, and peripheral ossifying fibroma. A provisional diagnosis of drug-induced gingival enlargement was made for the patient.

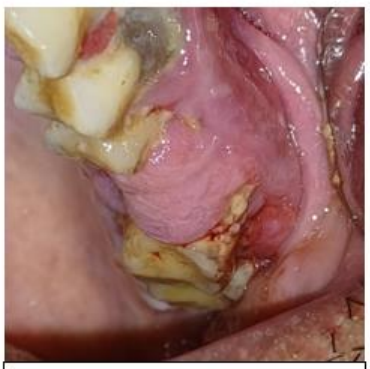

FIGURE 1: Gingival hyperplasia in the left posterior tooth region

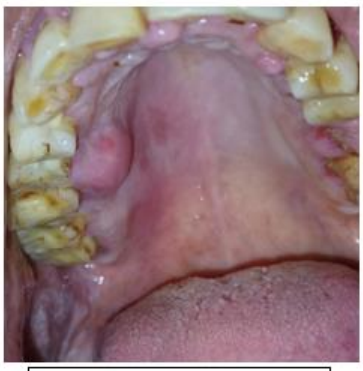

FIGURE 2: Gingival hyperplasia in the palatal aspect of right posterior tooth

Haematological examination with standard blood work was performed and all values were within normal ranges.

In the radiographic examination it is shown that, the overgrown gingiva on the surface of the tooth presents a reddish discolouration with enamel of normal hardness, there is lack of differentiation in the density between the enamel and dentine, intrapulpal calcification with hyperplastic follicles is noted.

The patient was advised to substitute or discontinue the medication in consultation with her physician. The growth was excised from the palatal aspect of maxillary molars and sent for histopathological examination (Figure 2), after which the area was sutured with 3-0 silk. Grossed tissue is about the size of 2.6 inches x 0.5 inches (Figure 3). The patient was recalled after 1 week for suture removal. At the 3-month recall, the patient showed significant resolution of gingival inflammation on the buccal and palatal aspect (Figure 2) and uneventful healing.

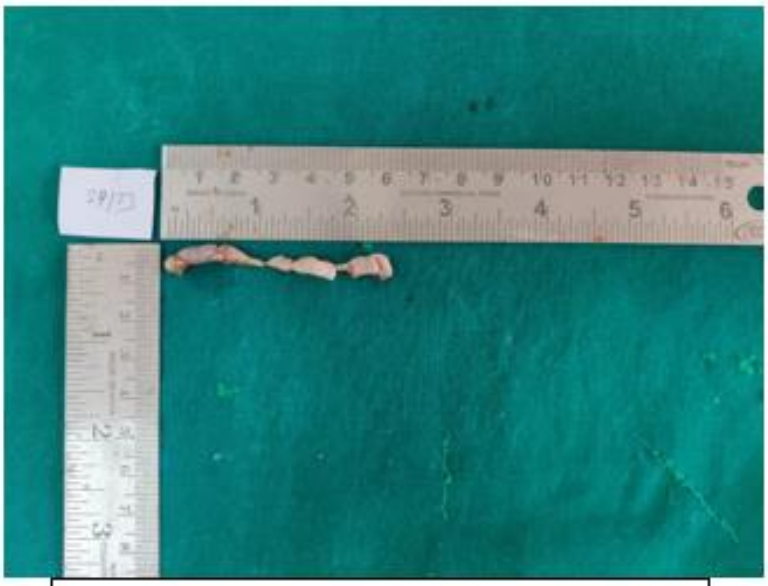

FIGURE 3: Grossed gingival tissue

Histological examination of the specimen demonstrated heavily inflamed connective tissue with prominent exuberant granulation tissue, no dysplasia or malignancy is noted (Figure 4,5,6,7). No lymph node is enlarged is noted. Histologically, the lesion was diagnosed as fibro epithelial hyperplasia, and was indicative of amlodipine-induced gingival hyperplasia based on clinical and histological evidence.

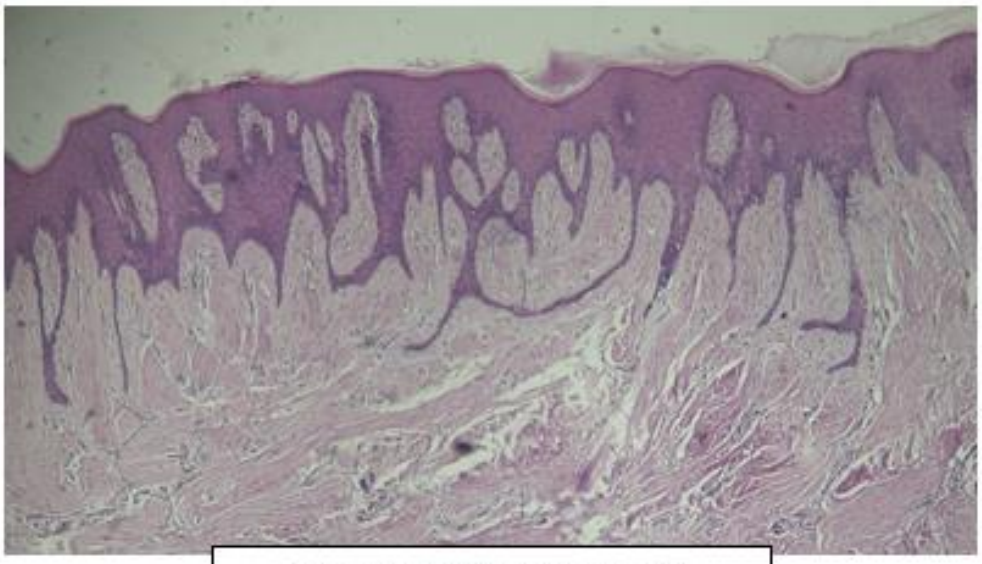

FIGURE 4: 4X Magnification

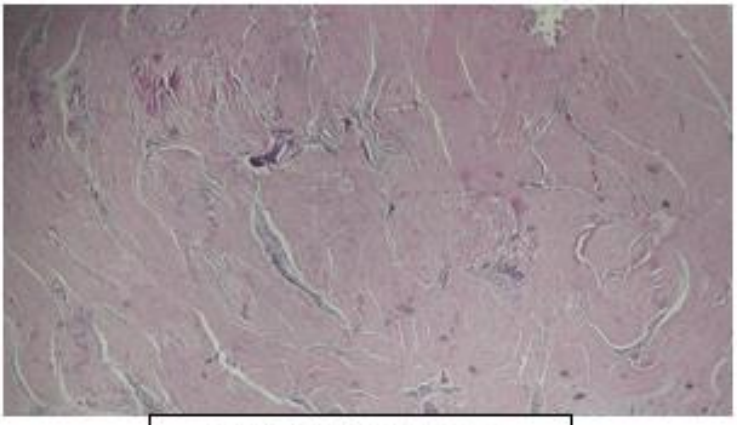

FIGURE 5: 10X Magnification

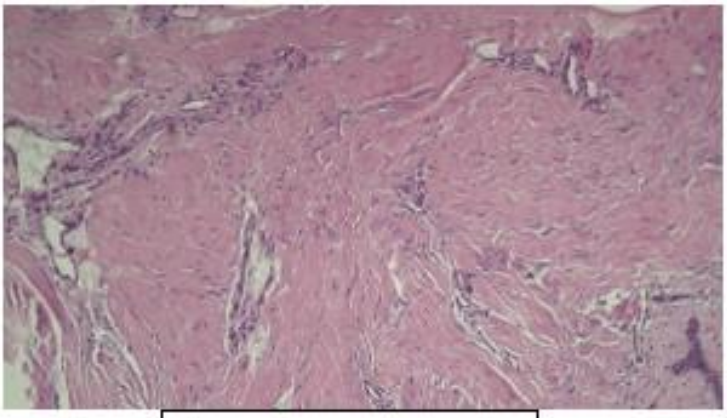

FIGURE 6: 40X Magnification

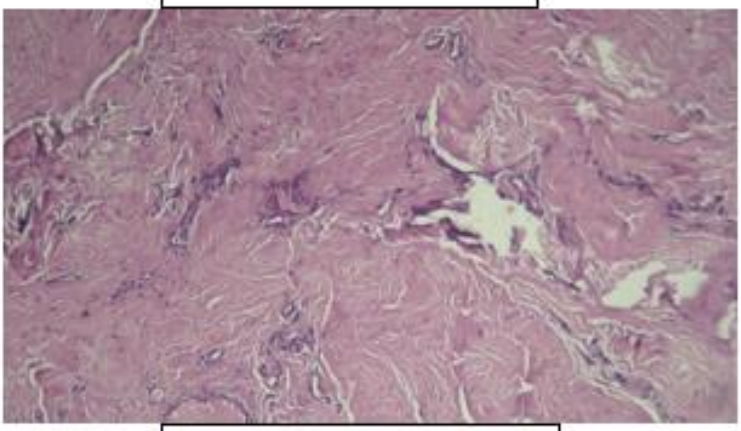

FIGURE 7: 40X Magnification

III. DISCUSSION

Gingival hyperplasia is one of the most concerning occurrences among hypertensive patients because of its cosmetic derangement and hindrance of oral function. Calcium channel blockers are one of the potential substances for gingival enlargement among various other drugs such as phenytoin and cyclosporine.[7] The incidence of nifedipine-induced gingival hyperplasia is about 10% which is comparatively more, amlodipine-related gingival hyperplasia is also common among individual who are prescribed with the drug. It is reported that in a series of 150 cardiac patients, who are prescribed with amlodipine 5mg/day the risk of gingival hyperplasia is not seen even after usage of more than 6 months.[4,8]

Gingival enlargements have various etiological factors including **inflammation**, systemic conditions such as **pregnancy**, **puberty**, **deficiency of ascorbic acid** and pathologies such as **leukaemia**, **sarcoidosis** and **Wegener's granulomatosis.[9]** They may be enlargements due to benign or malignant neoplasms or false enlargements of unknown origin.

As already stated **inflammatory induced gingival hyperplasia** maybe due to **chronic conditions of dental plaque** which presents as a ballooning enlargement of interdental papilla and marginal gingiva.[10] It can also be a sessile or pedunculated mass resembling a painless tumour. Histopathological features of such a type of enlargement show an exudative or a proliferative overgrowth with vascular engorgement, new capillary formation and associative degenerative changes.[11] Sometimes this type of changes are also seen in mouth breathers which is attributed to the irritation of surface dehydration. **Acute gingival inflammation** includes **gingival abscess** which is due a minor trauma to the periodontal tissue such as due to a toothbrush bristle or an apple core.[14] Conditioned enlargements like **pregnancy** induced gingival hyperplasia may present as a single mass or multiple tumour like masses. This is due to an excessive increase of oestrogen and progesterone levels which leads to changes in the vascular permeability resulting in gingival oedema and increased inflammatory response to dental plaque or any other minor trauma.[15] This type of enlargement varies considerably which is usually generalized and tends to be more prominent interproximally than on facial and lingual surfaces. On the other hand, a tumour like gingival enlargement referred to as **"pregnancy tumour"** is actually an inflammatory condition rather than a neoplasm.[16] This is usually presented after the third month of pregnancy. Gingival hyperplasia in pregnancy is also known as angiogranuloma. Histopathological findings of this type of enlargement include tumour-like enlargement of connective tissues and numerous diffusely arranged, newly formed, engorged capillaries lined by cuboidal endothelial cells. There is also the presence of moderately fibrous tissue with oedema and chronic inflammatory infiltrate.[17] The stratified squamous epithelium is thickened with more prominent rete pegs and intracellular and extracellular oedema, intercellular bridges and leukocytic infiltration. Gingival hyperplasia during **puberty** has all the clinical manifestations generally associated with chronic inflammation. The most important feature of this type of enlargement is its tendency to recur in the presence of relatively scanty plaque deposits.[18] This is a distinguishing feature between pubertal gingival hyperplasia and chronic inflammatory hyperplasia.

A study of subgingival microbiota of children **between ages of 11 and 14 years** and their association with clinical parameters implicated the Capnocytophaga species in the initiation of pubertal gingivitis.[19,20] Sone studies have also reported hormonal changes coinciding with increase proportion of P. Intermedia and Prevotella nigrescens.

One of the most important causes of gingival enlargement and gingival hyperplasia includes **vitamin C deficiency (scurvy)**. Vitamin C deficiency is not responsible in causing gingival inflammation but it causes gingival haemorrhage, collagen fibres degeneration, and oedema of the gingival connective tissue.[21] This alters the gingival response towards plaque and the extent of gingival inflammation gets massive due to exaggerated response and thus resulting in massive gingival hyperplasia. The histopathological features of this include chronic inflammatory cell infiltration with a superficial acute response. It also presents scattered areas of haemorrhage with engorged capillaries.[22] We can also notice marked diffuse edema, collagen degeneration and a scarcity of collagen fibrils and fibroblasts.

Plasma cell gingivitis is also another manifestation of gingival hyperplasia that is not only localised to the free gingiva but extends to the attached gingiva. The gingiva appears red, friable and granular. Gingival bleeding is common without any loss of gingival attachment. This type differs a lot from plaque induced gingivitis.[23] Histopathological figure represents the oral epithelium showing spongiosis and infiltration of inflammatory cells with signs of damage in the lower spinous layers and basal layers. The underlying connective tissue shows a dense infiltrate of plasma cells that also extends to the oral epithelium. Rarely, an inflammatory gingival enlargement with a predominance of plasma cells which is also associated with rapidly progressive periodontitis.

A non specific conditioned enlargement or **pyogenic granuloma** is also a tumour-like enlargement that is considered as an exaggerated response to minor trauma. It is also known as "pregnancy tumour". The treatment consists of the removal of the lesions plus the elimination of irritating local factors. The recurrence rate is about 15%.[24]

Some systemic diseases have also emerged as common causes of gingival hyperplasia such as **leukaemia** which may cause diffuse or marginal and localized and generalised. It appears as diffuse hyperplasia of the gingival mucosa or discrete tumour-like interproximal mass. The gingiva is generally bluish-red and has a shiny surface. It has a moderately-firm but there is a tendency towards friability and haemorrhage that occur either spontaneously or with slight irritation.[25] Some granulomatous diseases such as **Wegener's granulomatosis** is characterised by acute granulomatous necrotizing lesions of the respiratory tract and oral defects. The oral mucosa is the first area of defect noted which is manifested by oral mucosal ulceration, gingival hyperplasia, abnormal tooth mobility, teeth exfoliation, and delayed healing response.[26] The histopathological features include scattered giant cells., foci of acute inflammation and micro-abscesses covered by a thin, acanthotic epithelium. Vascular changes have not been described with gingival enlargement in patients with Wegener granulomatosis because of the presence of small sized blood vessels in the gingival connective tissue. It is an immunologically mediated tissue injury.[27] **Sarcoidosis**, on the other hand, also manifests gingival tissue as a red, smooth, painless

enlargement.[28] Here too, histopathological figure would present with discrete, non-caseating whorls of epithelioid cells and multinucleated and foreign body type giant cells and peripheral mononuclear cells.

Other systemic diseases include **Crohn's disease,** which presents as: the gingiva is pink, firm and almost leathery in consistency, with a characteristic minutely pebbled surface.[29] Signs and symptoms of these conditions must be strenuously trailed in these patients. It is normally associated with swelling of lips, bowel disorders, fever and ulcers. A consultation with gastro-enterologist will prove to be helpful. Some unusual presentations also include Generalized gingival enlargement has been rarely reported with **amelogenesis imperfecta**, **Hashimoto's thyroiditis, I-cell disease** and **multiple myeloma**.[30]

Gingival hyperplasia may also be a result of **neoplastic enlargements of gingiva**, an upcoming common cause of such a presentation. The examples include some benign tumours such as epulis which is used to address all discrete tumours and tumour-like masses of gingiva. In a survey of 257 oral tumours approximately 8% occurred on the gingiva. In another study of 868 growths of the oral mucosa (gingiva and palate), it showed that 57% of the lesions were neoplastic growths leaving the rest to be inflammatory. **Carcinoma** was found in 11%; **fibroma** as 9.3%; **papilloma** as 7.3%; **giant cell tumour** as 8.4%; **leukoplakia** as 4.9%; **angioma** as 1.5%; **sarcoma** as 0.5%; **osteofibroma** as 1.3%; **myxoma** as 0.45%; **melanoma** as 0.5%; **fibropapilloma** as 0.4%; **lipoma** as 0.3%; **adenoma** as 0.4% and **mixed salivary gland tumours** as 2.5%.[31]

Contrarily, Seymour et al. reported three patients with **poor periodontal conditions** who developed gingival hyperplasia upon a chronic usage (at least three months) of amlodipine. In case of our patient who used to take amlodipine 5mg OD for the last 8 years with poor oral condition and distinct oral lichen planus in right buccal mucosa posteriorly with history of burning sensation and also presence of tobacco pouch keratosis with chemical burns in lower labial mucosa and vestibule Amlodipine Induced Gingival Hyperplasia (AIGO) was present.[32] Presence of pocket with generalized recession and attrition was noted.[7]

The proposed **non-inflammatory mechanisms** as per Waxman et al (1970) include defective collagenase activity due to decreased uptake of folic acid, blockage of aldosterone synthesis in adrenal cortex and consequent feedback increase in ACTH level, and up regulation of keratinocyte growth factor (KGF).[33] Alternatively, inflammation may develop as a result of direct toxic effects of concentrated drug in crevicular gingival fluid (CGF) and/or bacterial plaques as stated in Ellis et al (1992) and Seymour et al (1994). This inflammation could lead to the up regulation of several cytokine factors such as TGF-ß1 causing an upregulation of fibroblast activity leading to increased collagen synthesis.[7,15,34]

In the present case the presence of inflammatory component parallels the presence of vertical gingival growth and consequently the presence of periodontal pockets or pseudo pockets. We hypothesize that the formation of pocket/pseudo pocket is a phenomenon that is associated with gingival inflammation.[35] So that, TGF-ß1 and other factors responsible for the production of a fibrous scaffold may be essential for the vertical growth of gingiva –pseudo pocket development- and also the formation of periodontal pockets necessitates the inflammatory degradation of the periodontal tissues. As an alternative, periodontal pocket formation may precede the inflammation.

As shown in the case study , gingival hyperplasia can also be a manifestation of **drug induced enlargement**. The most common drugs responsible include administration of some **anticonvulsants**, **immunosuppressants**, and **calcium channel blockers.[36]** The gingival growth starts as a painless, bead-like enlargement of the interdental papilla which then extends to the facial and lingual gingival margins. With progress, the marginal and papillary enlargements unite and develop into a massive tissue fold that covers a considerable portion of the crowns and interference in occlusion.[37]

Amlodipine is a dihydropyridine calcium channel blocker with structural similarities to nifedipine, which commonly causes gingival hyperplasia. From various reports, significant gingival overgrowth (SGO) is observed in about 6.3% and 1.7% of individuals taking nifedipine and specifically amlodipine, with a male preponderance. Amlodipine-induced gingival overgrowth is generally reported at a minimal dose of 10 mg/day within three months of drug initiation.[8,38]

Seymour and Preshaw et al. postulated that DIGO may have a **genetic predisposition**, given that among people using the same drug in the same amount or frequency, only some individuals develop DIGO; moreover, the severity of gingival overgrowth is different in different people.[39] Although different genotypes have been postulated, the exact genetic association has not been determined. It suggested that there is an association of gingival hyperplasia induced by calcium antagonists with genetic MDR1 polymorphism. In another study done by Thomason et al in 1996 in post-transplant patients, determined that patients with HLA-B37 are likely to be protected from gum hypertrophy following cyclosporine use and so experiences relatively less severe overgrowth than those who do not express this allele.[1,40]

Many studies have demonstrated a **drug-induced increase in glycosaminoglycans or connective tissue production secondary to gingival fibroblast proliferation**. Most of the increase in connective tissue is mediated by inflammatory cytokines, including interleukin-1 beta, interleukin-6, interleukin-8, tumor growth factor beta1, and prostaglandin E2, which are secreted as part of an inflammatory response to the drugs and lead to fibroblast

overgrowth. Cyclosporine inhibits the secretion of matrix proteases, contributing to the accumulation of extracellular matrix components in the gingival connective tissue, causing gingival overgrowth.[9,39,40]

Relevant doses of **cyclosporins** trigger gingival fibroblasts to exhibit significant reduced levels of matrix metalloproteinases-1 and -3 secretions which lead to accumulation of extracellular matrix components. 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 which converts inactive collagenase to active collagenase. Limited amount of collagenase becomes available.[10,41]

Among the various reviewed articles, several studies reported that drug discontinuation and periodontal therapy as an acceptable method of treatment for DIGO.[42]

A study reports a 75-year-old male suffering from hypertension and has a history of ischemic stroke was taking 40 mg of **nifedipine** daily, a conservative treatment plan was made, which includes oral hygiene instructions, scaling and root surface debridement, and suspension of nifedipine. They reported that at 11 weeks, the gingival overgrowth completely subsided.[43]

Another case report by Taib et al on 2007, reported a 55-year-old hypertensive female taking 5 mg of amlodipine daily presented with a massive gingival overgrowth and an inflamed interdental papillae. Their study reports that periodontal therapy alone without any drug intervention can yield satisfactory results.[44] **Surgical and CO2 laser gingivectomies** were done to the upper and lower arch. At a 2-year recall visit, the periodontal status was deemed satisfactory, and the patient was sent to a prosthodontist to fabricate a removable partial denture.

In our case report the patient came with a gingival overgrowth in the upper left and right buccal mucosa he gave a history of intake of **Amlodipine 5mg for 8 years**. He gave no history of pain or discomfort.[18,45] The patient underwent complete periodontal therapy and the patient is also referred to his designated medical practitioner for change in medication. At a six-month recall visit the periodontal status was gradually progressing and the gingival growth also decreased.

Approximately 40-50% of patients consuming phenytoin, cyclosporine, or calcium channel blockers will have development of some degree of gingival overgrowth. This condition can lead to problems with speech, mastication, tooth eruption, and aesthetics.[46] Controlling the inflammatory component through an appropriate oral hygiene program may benefit the patient by limiting the severity of the gingival overgrowth. In a patient in whom gingival overgrowth is present or may be anticipated, referral to a general dentist or periodontist is appropriate.[46] The physician's awareness of the potential for the development of overgrowth and the dental practitioner's role in attempting to prevent or minimize this problem are important aspects.

IV. CONCLUSION

Gingival enlargements can often be diagnosed by a careful history (e.g., drug influenced or hormonal influenced gingival enlargement), by location (e.g., mouth-breathing enlargement around anterior teeth) or by the clinical presentation (e.g., strawberry gingivitis). Presence of local irritants (plaque and calculus) could be primary or associated cause of gingival enlargements.[46] Hence, plaque control is an essential aspect of management in all the patients. An excisional/incisional biopsy and/or hematologic/histologic examination may be needed occasionally to correctly diagnose the uncommon cases of gingival enlargement. The clinician should have an open mind and consider all possibilities before coming to the final diagnosis of the condition at hand.[46]

Finally, we report that gingival hyperplasia is a possible side effect of amlodipine even with low dose administration when in conjunction with other aetiological factors such as plaque, calculus and tobacco use.

FOOTNOTES

CONFLICT OF INTEREST – NONE DECLARED

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