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Review article

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Gingival Overgrowth: Drug-induced versus Hereditary and Idiopathic

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Abstract

Gingival overgrowth (GO) is the abnormal enlargement of maxillary and mandibular gingiva. It can be caused due to different etiological factors inherited (hereditary) gingival fibromatosis (HGF), accompanied with diseases characterizing syndrome; idiopathic gingival fibromatosis (IGF) or as a side effect of an adverse drug reaction (ADR) known as drug-induced gingival fibromatosis (DIGF). The hypertrophic gingiva is also accompanied with variable growth factors expression at cellular and molecular levels. It is well observed in fibroblasts activity and production of collagenous fibers in connective tissues as well as their degradation. Thus, it would be useful to identify and explore different factors related to gingival growth changes to help in treatment plans. This review article will throw the light on systemic, pathological, histological and immuniohistochemical aspects associated with both HGF and DIGF.

Keywords: Gingival overgrowth; Hereditary gingival fibromatosis; Drug-induced gingival fibromatosis; Pathogensis; Histopathology; Immuniohistochemistry; Treatment

Introduction

Gingival fibromatosis, hypertrophic gingivitis, gingival hyperplasia or hypertrophy is the overgrowth of gingival (GO). Predisposing factors include inflammation, leukemia hormonal disturbances, uncontrolled diabetes and drug use [1]. It develops as slowly progressive, local or diffuse enlargements within marginal and attached gingiva or interdental papilla which might cover the crowns of the teeth in severe cases. Thus functional, esthetic, and periodontal problems, such as bone loss and bleeding might result due to the presence of pseudo-pockets and plaque accumulation. The most common forms of GO are those induced by systemic drugs (DIGO), (Table 1) [2]; followed by the inherited HGF or idiopathic IGF conditions [3]. Although many studies were devoted to studying the clinical aspects of GO, histological and molecular basis of both HGF and DIGO were not in their scope of interest. This review will focus on the pathogenesis, histological, molecular and regulatory mechanism that have been associated with both DIGO and HGF aiming at controlling the disease and amend about the approaches of its treatment.

Etiology

Enlargement associated with non-genetic diseases can be directly or indirectly linked to poor nutrition (vitamin C deficiency) [4], systemic hormonal stimulation (pregnancy or puberty) [5], leukemia [6,7], Wegener's granulomatosis [8], orofacial granulomatosis [9], pyogenic granuloma [10] and sarcoidosis [11]. It may also be associated with pseudotumors [12,13], benign neoplasms, e.g. giant cell fibroma [14], gingival and oral myofibroma [15,16], papilloma [17], giant cell granuloma [18], malignant neoplasms [19,20], salivary gland tumors [21,22], melanoma [23,24], adenoma and mucoepidermoid carcinoma [25].

Category	Pharmacologic agent
Anticonvulsants	Phenytoin
	Sodium valproate
	Phenobarbitone
	Vigabatrin
	Primidone
	Mephenytoin
	Ethotoin
	Ethosuximide
	Methosuxinimide
Immunosuppressants	Cyclosporin
	Tacrolimus
	Sirolimus
Calciumchannel blockers	Nifedipine
	Nitrendipine
	Felodipine
	Nicardipine
	Manidipine
	Amlodipine

Table 1: Drugs causing gingival overgrowth.

Gingival enlargement may develop during the course of inflammatory diseases of the oral cavity, e.g. localized and generalized aggressive periodontitis, primary gingival tuberculosis [26,27],

inflammatory pseudotumors [13] and inflammatory fibrous hyperplasia due to local irritants [28]. Plaque accumulation and bacterial infection resulting from poor oral hygiene are significant predisposing factors [29,30].

Gingival enlargement might be associated with hereditary factors or co-existing with genetic diseases and syndromes [28,31,32]. Despite the pharmacological heterogeneity of the three major drugs causing GO, immunosuppressants, calcium channel blockers and anticonvulsants (Table 1) still they possess similar mechanism of action at the cellular and molecular levels; leading to DIGF [33,34]. This occurs by inhibiting the intracellular calcium influx, hence having a common side effect upon gingival connective tissue. Immunosuppressive drugs as cyclosporine and tacrolimus have immunosuppressive properties and as consequence they may protect the patients against periodontal breakdown [35]. However, gingival enlargement might be of unknown etiology [36,37].

Pathogenesis

It was observed that children and adolescents are more subjected to DIGF than adults. It was postulated that drug-induce an influence on androgen and testosterone metabolism which could be a significant factor in the pathogenesis of drug induce gingival overgrowth. Likewise, excised tissue from nifedipine and cyclosporine-induced GO demonstrates a similar increase in androgen metabolism [35].

The active androgen metabolites could target gingival fibroblasts and cause either an increase in collagen synthesis or a decrease in collagenase activity.

It was reported that a certain threshold concentration of the drug or its metabolites is necessary to activate gingival fibroblasts. Moreover, it was obvious that there is a direct relation between salivary cyclosporine or phenytoin and gingival overgrowth [35]. Recent attention has focused on local drug concentration in gingiva.

Phenytoin (anticonvulsant) was first introduced in 1938 as an antiepileptic drug but due to its adverse side effects leading to a significant gingival overgrowth; other anticonvulsant agents were introduced as shown in Table 1.

These drugs have been linked to clinically significant forms of GO [38]. Though, cyclosporine is widely used in tissue rejection prevention after transplantation, it might have damaging side effects such as nephrotoxicity, hepatotoxicity and gingival fibromatosis [39].

Recently, tacrolimus or FK506 is considered as an alternative to cyclosporine, since its side effects are less severe with frequent association of GO with its use [40].

Extracellular matrix (ECM) plays an important role in the regulation of cell functions, storage for various growth factors and participation in the regulation of their activation. Thus, altered abundance or composition of ECM may play an active part in the pathogenesis of GO [41]. Collagen type-1 which is considered as the major component of EMC, is evaluated by observing the balance between its synthesis and degradation intercede by matrix metalloproteinases (MMPs) and tissue matrix metalloproteinase inhibitors (TMPIs) [42-44].

The connective tissue turnover is largely controlled by chemokines and cytokines. It was observed that high levels of specific cytokines as transforming growth factor TGF-B, platelet drive growth factor B (PDGF-B), fibroblast growth factor-2 (FGF-2) and connective tissue growth factor (CTGF) are increased in patients treated with immunosuppressive, anticonvulsants and calcium channel blocker drugs.

It has been confirmed that exposure of gingival fibroblasts to different drugs as cyclosporine increases the level of transferable collagen RNA causing an overproduction of collagen and hence inducing gingival enlargement. At the same time gingival fibroblasts are heterogeneous in respect of their ability to synthesize collagenase and TMP which may be affected by drug induction.

Regarding (HGF), the pathologic manifestation of GF is correlated to the excessive accumulation of ECM and proteins, including collagen type I [45,46]. During collagen biosynthesis, single procollagen polypeptides undergo post-translational modification in the endoplasmic reticulum (ER), forming triple-helical chains, which are then secreted into the extracellular space. This process involves heat shock protein 47 (HSP47), a 47 kDa glycoprotein localized in the ER.

It binds to type I procollagen peptides to prevent premature folding and aggregation of procollagen chains, and participates in the translocation and secretion of procollagen I into the extracellular space result in subnormal gingival growth [47].

Fibroblast cultures from patients with HGF exhibited high levels of type I collagen and HSP47, mRNA and protein [48]. Moreover, transforming growth factor (TGF)-β 1 and interleukin (IL)-6 induce the expression of type I collagen and HSP47 and downregulate matrix metalloproteinase MMP-1 and MMP-2 in fibroblast cultures from HGF patients. On the other hand, interferon-γ (IFN-γ) reduced collagen I and HSP47 expression, and slightly affected MMP-1 and MMP-2 [48]. This observation suggests that HSP47 might be a crucial molecule in the post-translational processing of the overproduced type I procollagen chains, while enhanced TGF-β 1 and IL-6 production in patients with GF may favor the accumulation of collagen fibrils in the gingiva.

MMPs are key enzymes regulating the composition of the ECM; thus the alteration in their expression has been implicated in the pathogenesis of GF. Several studies showed a significant decrease in the expression and activity of MMP-1 and MMP-2 in fibroblasts from HGF patients [48,49].

MMP-1 is a collagenase that degrades interstitial collagen, while MMP-2 acts predominantly on type IV collagen, but it has also been shown to degrade type I collagen [50]. Similarly, the inhibition of MMP-1, MMP-2, and MMP-3 has been reported, a condition also associated with enhanced TGF-β1 production [51,52]. The catalytic activity of the MMPs is regulated at the transcriptional level as well as by TIMPs. Coletta et al. [49] concluded that the addition of anti-TGF-β1 antibodies resulted in a slight increase in MMP-1 and a decrease in MMP-2 expression, whereas TIMP-1 and TIMP-2 expression were unaffected. These results confirm previous observations that enhanced TGF-β1 production may lead to the accumulation of ECM by altering the proteolytic activities of fibroblasts (Figure 1).

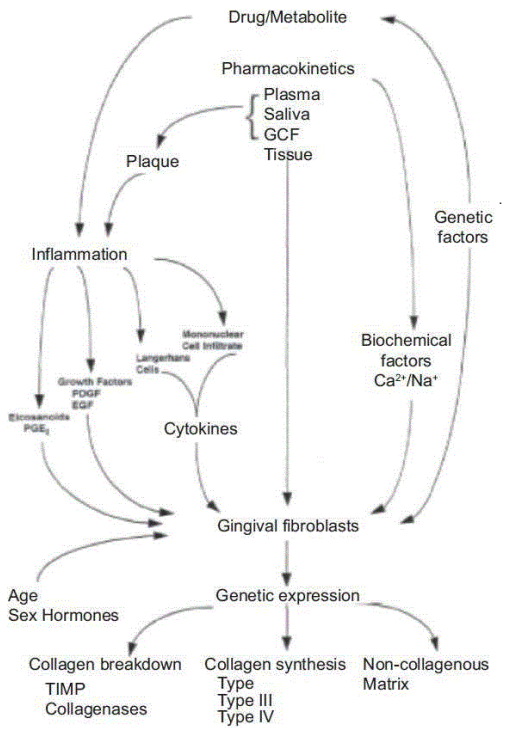

Figure 1: Schematic diagram to illustrate the potential multifactorial features and interactions involved in the pathogenesis of drug-induced gingival overgrowth.

Genetic Predisposition

Although, the hereditary condition of HGF exhibits autosomal dominant mode of transmission, an autosomal recessive inheritance has also been reported [53]. Gingival fibromatosis may be familial or idiopathic [2].

The familial variation may occur with a number of other inherited syndromes; e.g. Zimmerman Laband syndrome, [54,55] Murray Puretic drescher (juvenile hyaline fibromatosis) [55].

Rutherfurd, Cross, Cowden syndrome, multiple hamartomas, tuberous sclerosis [56,57] and HGF may be associated with other clinical manifestations such as hypertrichosis, [58] growth retardation, [59] hypopigmentation, mental deficiency, [60] epilepsy, [61] splenomegaly, [54] optic and auditory defects, cartilage and nail defects and dentigerous cysts [62].

The most common syndrome of HGF includes hypertrichosis, epilepsy and mental retardation, however the two latter features were not present in all cases [63]. Autosomal dominant forms of gingival fibromatosis, which are usually non-syndromic, have been genetically linked to the chromosome 2p21-p22 and 5q13-q22 [57].

A mutation in the Son of Sevenless 1 (SOS-1) gene has been suggested as a possible cause of non-syndromic gingival fibromatosis, but no definite linkage has been established yet [57]. Two genetically distinct loci seemed to be responsible for this type of HGF [64], though a locus for autosomal dominant HGF has been mapped to a region on chromosome 2 [65].

Hiura et al, [66]; Landstrom and Ackerman, [67] reported that most common diseases are recognized to have an inherited genetic susceptibility, which leads to disease onset when combined with environmental factors. Traits for several uncommon dental diseases such as amelogenesis imperfecta or pre-pubertal periodontitis are inherited in an autosomal dominant or recessive pattern [68-70].

In these cases, a single gene defect is responsible for disease occurrence, being potentially targetable by specific management strategies once the genetic mutation is identified. Three genetic defects on chromosome 2 and 5 have so far been identified as responsible for HGF [71-73]. Thus, a whole-exome or whole-genome sequencing will be needed to identify the mutation causing HGF in a certain family.

This technology will also address the remote possibility of an X-linked recessive inheritance because all genes on all chromosomes are sequenced and can therefore be assessed for variants on the X-chromosome.

On the other hand, evidence from previous researches postulated that individual susceptibility to drug may be related to genetic predisposition variation in drug responsive and tolerance, as well to different drug concentration which in turn play an important role in the decrease or increase of fibroblasts proliferation and hence lead to (GO) [74,75].

Gingival overgrowth individual susceptibility (GOIS) may be related to genetic predisposition where gingival fibroblasts exhibit functional heterogeneity in response to various drug stimulation. Several drugs as cyclosporine lead to increase synthetic activity of the fibroblasts and decrease collagenolytic activity as expressed by collagenase and TMPI production [76].

This may be influenced by drug receptor binding, drug metabolism, collagen synthesis and many other factors. Human Lymphocyte Antigen (HLA-DR1) and (DR2) expressions may prove to be a useful genetic markers for the identification of patients with high risk of developing drug-induced gingival overgrowth.

Clinical Description

Clinically, the onset coincides with the eruption of primary or permanent dentition, and rarely presents at birth [77]. GF may also occur as a local, nodular-like lesion.

In severe cases, the excess gingival tissue can cover part of or the entire crown, and can result in diastemas, teeth displacement, or retention of primary or impacted teeth, and may also cause masticatory, phonetic, psychological, and esthetic problems [78].

Unlike DIGO which usually occurs as a generalized diffuse enlargement, HGF is characterized by a slow, progressive growth of the gingival tissue (Figures 2 and 4).

This enlargement may project into the vestibule and floor of the mouth; interfere with normal mastication and even lip closure that makes the speech difficult. The enlarged gingival tissue appears firm and pink with exaggerated stippling [2,70].

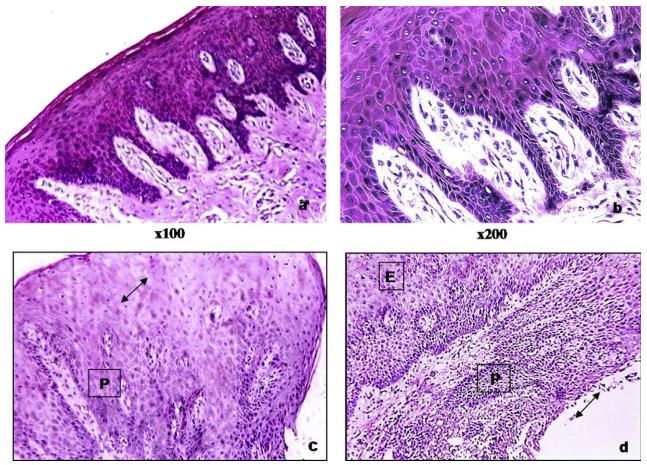

Figure 2: Photomicrograph of gingival section of (a, b) HGF Gp showing mild hyperplastic stratified squamous epithelium with elongated rete-ridges showing a tubular pattern. c) CsA treated group showing pronounced increase in epithelial thickness (hyperplasia) (E), marked elongation of papillae (P) and hypertrophy of epithelial lining mucosa. d) Mild hyperplasia (E), notable elongation of papillae (P), and mild degenerative areas (The figures showed difference in Epithelial and connective tissue structure in both DIG and HGF).

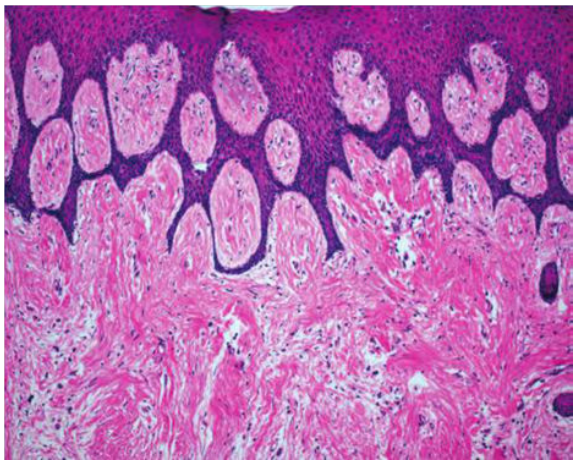

Figure 3: Photomicrograph of HGF tissues shows a dense connective tissue predominantly consisting of thick and irregularly arranged collagen fibers underlying an epithelium with elongated rete pegs (hematoxylin and eosin stain; original magnification X100).

The gingival hyperplasia may be generalized (symmetric) or localized (nodular) [79]. Local involvement mainly affects the maxillary tuberosity's and lingual surfaces of lower molars and is typically characterized by the presence of multiple large masses [2,80].

On the other hand, the symmetric form, which is the most common type of disorder, results in uniform enlargement of the gingiva that is firm, dense, tough resilient, insensitive fibrous tissue that covers the alveolar ridges and extends over the teeth resulting in extensive pseudo pockets [81].

Histopathological Description

Hyperplastic epithelium with elongated rete ridges extending into the underlying connective tissue is the typical histopathological feature of the lesion [69,82]. The connective tissue consists of excess collagen, but it has relatively few fibroblasts and blood vessels [83,84]. Enlarged fibroblasts appear scattered among thin and thick collagen fibrils.

It appears that the human gingival fibroblasts from hereditary fibromatosis tissue exhibit characteristics of permanently activated fibroblasts as they grow faster and produce more collagen and fibronectin than fibroblasts from normal human gingiva [84]. Elastic and oxytalan fibers are also present. Unlike in normal gingiva, coarse and fine dense collagen fiber bundles are oriented in all directions [36, 85-87].

Small osseous calcifications and abundant neurovascular bundles might also be present. Overgrowth of the gingival tissue might provide a chance for the growth of microorganisms, plaque accumulation and pseudo pockets formation resulting in inflammatory infiltration of the gingival connective tissue [88-89].

The histopathological appearances of the various DIGO are somehow similar regardless of few differences as appeared in (Figure 2c and 2d). The potential drug related difference has been described only when different staining techniques have been employed. The epithelial acanthuses observed in DIGO may be due to an entranced keratinocyte life spam by the action of drugs. Epithelial hyperplasia and elongated papillae observed in drug induced gingiva may suggest that the increase in epithelial tissue observed, is a result of direct effect of drugs on epithelial cells [35].

However an indirect result of drug interactions with other cells in the gingival tissues as fibroblast cells in the underlying connective tissue may play role in the GO. The close relation between the epithelial and its adjacent connective tissue in their development has been the subject of strong examination. The interaction between both was mediated by two growth factors keratinocyte factor (KGF) and Scatter Factor (SF) in mesenchymal cells in close vicinity to epithelial structure [41-44].

Gingival fibroblasts are capable of synthesizing both FGF and SF. Recent studies show the increase of KGF and its receptor (KGF-R) in pathological over grown gingiva compared with normal gingival tissue. Thus it was suggested that epithelial changes in gingiva accompanied with drug induction is considered as secondary alteration due to abnormalities drug induced in the underlying lamia propria and mainly the adverse effect on fibroblast and growth factors.

A recent study using immunohistochemical stain for different growth factors, showed variability in concentration of these growth factors (TGF-ß1, PDGF-ß, TMPI and MMP) in relation to different drugs induced gingival over growth [62]. It was observed that not all drugs induce an adverse effect on gingiva, causing a significant overgrowth. The different results of both immunosuppressive drugs cyclosporine and tacrolimus showed that tacrolimus must be used in favor of cyclosporine [35].

Treatment

The patient's management depends on: a) The medical history (e.g. patient's age and the presence of other diseases) b) The clinical examination c) The size of the gingival overgrowth. Accordingly, when the enlargement is minimum, good scaling of the teeth, oral hygiene instructions and administration of antibiotics, usually amoxicillin and metronidazole, along with anti-inflammatory (ibuprofen) and analgesic (paracetamol) drugs and the use of chlorhexidine mouth rinses may be essential. The use of azithromycin in the management of GO was recently reported by researchers. The use of nonsteroidal anti-inflammatory agent could be used to control interlukin-1 thus mediating inflammation as well low dose of androgen receptors antagonists to block the receptors of androgen and hence decrease abnormal collagen production (Figure 4). Furthermore, the discontinuing of using certain drug or using alternative medication replacing the used ones is sometimes required. Phenytoin was replaced by sulthiame and topiramate and cyclosporine-induced gingival fibromatosis was substituted by tacrolimus. Also, azathioprine was used as a protective drug against gingival hyperplasia through its anti-proliferative and anti- inflammatory effect [89].

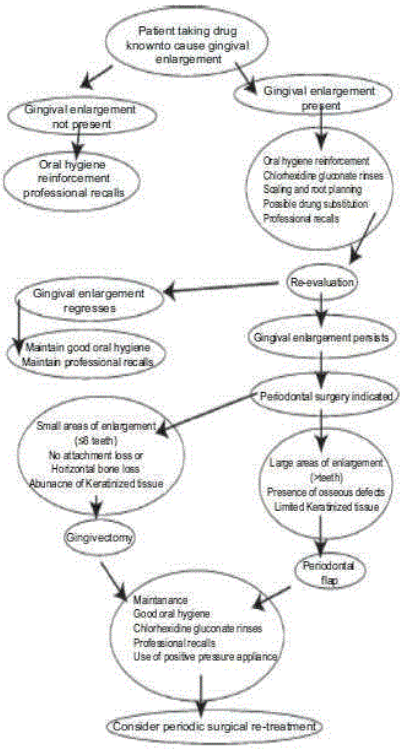

Figure 4: Decision tree in the treatment of drug-induced gingival overgrowth.

When the gingival mass increases; the need for surgical intervention is required owing to the functional and esthetic compromise. The treatment consists of surgical excision of the enlarged tissue; often in a series of gingivectomies, that should be accompanied by an effective program of oral hygiene. Few studies have documented the use of carbon dioxide laser, [48] however; the most widely used method of removing large quantities of tissue is the conventional external bevel gingivectomy with gingivoplasty particularly when there are pseudo pockets and no attachment loss [88,89]. A periodontal flap procedure may be preferred if fibromatosis is accompanied by attachment loss and osseous defects [80]. While non-specific gingival surgical excisions are the standard treatment for HGF, interferon-gamma is an example of a potential therapeutic adjunct for HGF cases, because of its activity on fibroblast myofibroblast differentiation [89]. Whenever possible the treatment should be performed after the complete eruption of permanent dentition. Regenerative techniques include the use of bone grafts, barrier membranes, wound healing agents and enamel matrix protein.

It has been reported that recurrence might be a common feature over varying periods. One report indicated that there is less chance of recurrence if the gingivectomy is delayed until permanent dentition is in place [58]. However slight recurrence was seen after 20 months [89]. In several reported cases, there was no recurrence in a period of 2 years, [81] 3 years, [82] or even 14 years follow up [83].

Conclusion

GF is a rare and slowly progressive condition that is also characterized by etiological heterogeneity. Moreover, it constitutes a typical symptom of several genetic syndromes and may occur sporadically in several other syndromes and diseases. By contrast, DIGO may occur as soon as several months from the onset of systemic therapy in susceptible individuals treated with certain immunosuppressant's or calcium channel blockers. DIGO and HGF are disorders characterized by varying degrees of attached gingival overgrowth which might cause masticatory, phonetic, psychological, and esthetic problems. In general, the histological features of GF are similar, but phenytoin-induced GO is reported to be most fibrotic and to express higher levels of CTGF than nifedipine and CsA-induced GO. Excessive accumulation of ECM components, particularly collagen type I, seems to contribute to the pathologic manifestation of all etiological types of GF. Understanding of the molecular mechanisms leading to this disease may give better options for possible novel management strategies and allow the implementation of less invasive therapeutic methods than surgery into routine dental practice. In the current review, we tried to verify the various conditions of GF and focus mainly on their pathogenesis, histopathological, and regulatory mechanism as an overview and in an attempt for controlling the disease.

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