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Comprehensive Insights into the Etiologies and Treatment of Gingival Hyperplasia

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Abstract

Gingival hyperplasia represents a heterogeneous group of pathologic overgrowths of the gingival tissues, characterized by excessive accumulation of extracellular matrix components, primarily collagen, and variable degrees of inflammatory infiltration. Although traditionally considered a localized oral condition, the etiologies of gingival hyperplasia are increasingly recognized to reflect an interplay between genetic, pharmacologic, systemic, and local inflammatory drivers. Drug-induced gingival overgrowth remains a predominant category, particularly with chronic use of calcium channel blockers, anticonvulsants such as phenytoin, and immunosuppressants including cyclosporine. Specific pharmaceutical agents induce fibroblast proliferation and collagen deposition via distinct molecular pathways involving TGF-β signaling, MMP inhibition, and altered epithelial–mesenchymal interactions. Inherited forms of gingival fibromatosis, frequently associated with syndromic presentations such as Zimmerman–Laband or Rutherford syndrome, further implicate dysregulation of fibroblast function and aberrant mesenchymal differentiation. Inflammatory etiologies, including chronic plaque-associated gingivitis and periodontitis, act as cofactors or independent triggers in susceptible individuals, amplifying the fibrotic and angiogenic response. Recent findings also highlight the role of hormonal fluctuations, hematologic malignancies such as leukemia, and systemic conditions including granulomatosis with polyangiitis in the development of secondary gingival overgrowth. Management strategies must be tailored to the underlying cause, with a combination of meticulous plaque control, drug substitution, surgical intervention through gingivectomy or flap procedures, and adjunctive use of lasers or antifibrotic agents. Molecular-targeted therapies, including modulation of cytokine pathways and antifibrotic pharmacologics, represent promising areas for future treatment modalities. Defining the molecular distinctions amongst inflammatory, pharmacologic, and genetic subtypes of gingival hyperplasia will enable the development of targeted therapies that move beyond surgical containment toward biologically driven disease modification and long-term prevention..

Keywords: *gingival hyperplasia, gingival hypertrophy, drug-induced gingival overgrowth, molecular pathogenesis, gingival fibromatosis, targeted therapies*

1. INTRODUCTION

Gingival hyperplasia describes a heterogeneous group of pathologic overgrowths of gingival tissue, notably characterized by the accumulation of collagen and various inflammatory infiltrates [1]. Gingival hyperplasia can also be known as gingival overgrowth, gingival hypertrophy, and hyperplastic gingivitis.

Its clinical presentation can vary from being very subtle or pronounced proliferation, occasionally resulting in full coverage of dental tissue. The etiopathogenesis of gingival hyperplasia is a multifactorial combination of molecular and cellular mechanisms [2]. Most commonly, gingival overgrowth can be a result of the use of systemic drugs like anticonvulsants (phenytoin), immunosuppressants such as cyclosporine, and calcium channel blockers like nifedipine [3]. Other reported categories of gingival hyperplasia include hereditary, idiopathic, and inflammatory [4]. Inflammatory gingival hyperplasia can be

due to hormonal changes and manifests as reactive oral mucosa with fibrous and granulation tissue [5]. Additionally, no matter the pathogenesis, all studies show the involvement of dental plaque [6]. Given its varied presentations and multifactorial causes, understanding the underlying etiology of gingival hyperplasia is essential for accurate diagnosis and effective management.

Despite gingival hyperplasia being a mostly benign condition, it can significantly impact patients' lives by impacting aesthetics, daily function, and periodontal issues [7]. Given its visible and sometimes disfiguring presentation, gingival hyperplasia holds clinical relevance not only in dental practice but also in dermatology, where mucocutaneous manifestations may overlap or be mistaken for other conditions. The multiple etiologies of gingival hyperplasia and how it impacts patients warrant proper treatment and a holistic understanding of therapies. Initial treatment is often nonsurgical and includes appropriate plaque control with adequate oral hygiene, discontinuation or modification of the offending medication, and/or the addition of antibiotics to control inflammation [8]. Drugs targeting proteins involved in fibrosis such as transforming growth factor (TGF) and endothelin-1 (ET-1), among others, are being explored to reduce gingival overgrowth and prevent recurrence [9]. Other forms of treatment include bacterial decontamination and surgical excision with laser therapy [10]. By better defining the molecular distinctions among the different etiologies of gingival hyperplasia and current therapies, clinicians can move toward more personalized, effective treatment approaches that address both the underlying cause and the patient's functional and aesthetic concerns. This review aims to synthesize current knowledge on the etiologies, clinical implications, and treatment strategies for gingival hyperplasia, with a particular emphasis on highlighting molecular changes and therapies to optimize patient outcomes

2. DISCUSSION

2.1. Etiopathogenesis

2.1.1. Drug-Induced Gingival Overgrowth

Drug induced gingival overgrowth (DIGO) is a complex condition commonly associated with certain medications, such as calcium channel blockers (CCBs), phenytoin, and cyclosporine. Veena et al. (2025) highlighted a 70% prevalence of gingival hyperplasia among patients taking phenytoin, strongly linking DIGO and individuals taking anticonvulsants. The pathogenesis of DIGO involves drug-specific interactions with gingival fibroblasts, leading to excess ECM accumulation, primarily composed of collagen. Phenytoin, for instance, upregulates periostin in human gingival fibroblasts via a TGF-B dependent pathway, leading to ECM deposition, through SMAD3 phosphorylation (Kim et al., 2013). Similarly, cyclosporine A, a calcineurin inhibitor used as an immunosuppressant, leads to gingival fibroblast proliferation by upregulating CDC25A and CYCLIN E1 and downregulating SMAD3 and SMAD4, thereby bypassing G1 cell cycle arrest. Cyclosporine A's molecular effects highlight the role of cell cycle dysregulation in the pathogenesis of DIGO. Chung et al. (2013) proposed a hierarchical crosstalk between TGF-B and Sonic hedgehog (Shh) signaling pathways, with cyclosporine permitting enhanced expression of both in gingival fibroblasts. TGF-B upregulates Shh expression, leading to increased fibroblast proliferation.

Extending beyond fibroblast stimulation, impaired matrix remodeling and epithelial-mesenchymal interactions are extensively involved in the pathogenesis of DIGO. Li et al. (2015) reported that Nifedipine has shown to exacerbate gingival enlargement not only through fibroblast-related pathways, but also by disrupting ECM turnover. Inhibition of matrix metalloproteinases (MMPs) such as MMP-2 and MMP-9 has been observed in DIGO, and have resulted in reduced collagen degradation and ECM accumulation (Li et al., 2015). Additionally, Das et al. (2002) reported increased expression of keratinocyte growth factor receptors in gingival tissues affected by cyclosporine A, suggesting increased epithelial-mesenchymal transition. Kantarci et al. (2011) provided evidence of basement membrane disruption and reduced laminin 5 expression, which permits epithelial cell migration into connective tissue and contributes to fibrotic remodeling through the epithelial-mesenchymal transition. Drug-induced gingival overgrowth incorporates both impaired matrix turnover and irreversible epithelial changes, which sets a base understanding for other fibroproliferative conditions such as hereditary gingival fibromatosis.

2.1.2. Hereditary Gingival Fibromatosis

The most common genetic form of gingival fibromatosis is hereditary gingival fibromatosis (HGF), and is characterized by a steadily progressing benign enlargement of the keratinized gingiva. HGF is genetically

heterogeneous, and can be inherited as either autosomal dominant or autosomal recessive, and in some cases, may appear sporadically (Bayram et al., 2017). Different forms of HGF, such as Zimmermann-Laband syndrome, occur with anomalies such as nail hypoplasia, and have been linked to pathogenic mutations in genes like KCNH1, KCNN3, and ATP6V1B2 (Gu et al., 2024). Similarly, another subtype, Rutherford syndrome presents with gingival fibromatosis, corneal dystrophy, abnormally shaped teeth, and delayed eruption, and is associated with connective tissue disorders (Raja et al., 2008). These syndromes display the importance of recognizing syndromic features in patients presenting with gingival enlargements, as they may signify systemic involvement. At the cellular level, HGF is characterized by fibroblast dysregulation. Zhu et al. (2024) reported the association with HGF and a ZNF862 mutation, highlighting the role of ZNF862 as a transcription factor that inhibits human gingival fibroblasts through inhibition of cell proliferation via the p21-RB1 signaling pathway. ZNF862 also promotes HGF apoptosis by enhancing the Bcl-xL-Caspase 3 signaling pathway. Faulty defects in the ZNF862 protein can lead to uncontrolled HGF proliferation. Additionally, Gao et al. (2021) reported that activation of the KCNQ1 potassium channel promotes fibrogenic responses in normal human gingival fibroblasts, linking mesenchymal signaling to tissue overgrowth. Epithelial-mesenchymal transition adds further layers of complexity to mesenchymal differentiation, amplifying fibrotic changes in affected gingiva. Taken altogether, key molecular pathways in HGF include the ECM-receptor interaction pathway, the TGF-B signalling pathway, and the cell adhesion molecule (CAM) pathway. Additionally, hub genes such as CDH1, SNAP25, RAC2, APOE and ITGB4, which are associated with cell adhesion, were identified to be key regulators in the fibrotic aspect of HGF (Yang et al., 2024). These findings emphasize HGF's genetic and molecular complexity beyond its structural anomalies.

2.1.3. Inflammatory Etiologies

Inflammatory processes tend to heavily cater to the pathogenesis of gingival overgrowth, especially in the context of chronic plaque-associated gingivitis. Dental plaque biofilms interact with the host's inflammatory response, resulting in localized epithelial proliferation and fibroblast activation, limited to the gingival site (Chapple et al., 2018). Proinflammatory cytokines such as IL-1B and IL-6 can initiate changes at the tissue level, regardless of genetic or pharmacological factors. Even at an early stage, periodontitis causes destruction at an epithelial level by introducing bacterial endotoxins and proteases that prolong inflammation and cause destruction, as seen by elevated levels of fibrinogen and CRP (George et al., 2025). Porphyromonas gingivalis and other pathogens regulate local immune responses and matrix turnover, often disrupting tissue homeostasis and promoting imbalance. Martinez-Garcia et al. (2021) reported that periodontal inflammation was linked to the upregulation of genes associated with fibrosis and signaling. This supports that periodontitis may be an active driver of fibrotic gingival changes. These findings link chronic inflammation–whether from a plaque, immune dysfunction, or an infectious source–to an ideal environment for sustained gingival enlargement and tissue proliferation. Effective plaque control is essential to both preventing diseases by periodontal pathogens and reversing gingival overgrowth in predisposed patients.

In addition to immune activation, chronic inflammation also promotes angiogenesis and fibrosis, which contribute heavily to gingival overgrowth. Elevated IL-6 family cytokine expression, particularly oncostatin M, has proven to contribute to extracellular matrix accumulation and angiogenic activity (Gurkan et al., 2015). This remodeling facilitates fibroblast proliferation and collagen deposition. Through transcriptome analyses, Kebschull et al. (2014) emphasized the role of inflammatory mediators in fibrotic remodeling by demonstrating the enrichment of TGF-B signaling and angiogenesis-related pathways in inflamed gingival tissues. Even under host-derived stressors like sapienic acid, P.gingivalis remains persistent and continues to have an inflammatory impact by undergoing changes in bacterial membrane proteins, stress pathways, and antioxidant systems (Fischer et al., 2015). These microbial adaptations contribute to long-term tissue damage and prolong the inflammation causing gingival hyperplasia. Lastly, Chen et al. (2023) studied renal transplant recipients and highlighted that gingival tissues exposed to chronic inflammation tend to alter fibroblast gene expression along with cytokine profiles. These findings emphasize the inflammatory microenvironment's complexities by incorporating the immune, vascular, and stromal aspects altogether. Rather than solely relying on surgical interventions, it is

vital to understand these dynamics in order to produce targeted quality treatment that attacks the pathophysiological mechanisms of inflammatory gingival enlargement.

2.1.4. Systemic and Other Contributing Factors

The physiopathological mechanisms in which gingival hyperplasia manifests often encompasses a wide range of systemic contributing factors. Hematologic malignancies, significant hormonal influence, and, to a lesser extent, conditions such as granulomatosis with polyangiitis have been linked to gingival hyperplasia. For instance, during pregnancy, the concurrent rise in progesterone and estrogen, alongside a heightened immune response, increases the susceptibility of subgingival microflora to become encapsulated by periodontally destructive species [30]. This notion is supported by Beaumont et.al (2017), a study that emphasizes increased vulnerability to intracellular pathogens such as *P. gingivalis* and *P. intermedia* which avoid host defenses [31]. Concomitant to the rise in pregnancy hormones, there is an increase in gingival inflammation and poor alterations of healthy tissue growth [Beaumont et al., 2017]. Similarly, in both male and female adolescents, the variation in steroid sex hormones during the pivotal time of puberty may influence the synthesis and maintenance of keratinocytes, collagen, and fibroblasts which further pose implications on gingiva [Markou, 2009]. Markou et. al (2009) reported that some species of bacteria tend to take advantage of the markedly elevated sex hormone levels—testosterone in males and estrogen and progesterone in females—triggering a hyperplastic response in the gingiva, particularly in areas where food debris, plaque, and calculus accumulate [32].

The overlap between gingival enlargement and hematologic malignancies such as leukemia has also been closely studied. Although hematological disorders encompass a broad spectrum of diseases, they typically affect the health of gingiva based on weakened immune system, increased risk of bleedings, side effects of therapy and changes in composition of blood [Łobacz, 2024]. Łobacz et. al (2024) emphasizes how cases of leukemia and lymphoma in particular disrupt the host immune system, particularly in association with neutropenias, increasing the oral cavity's vulnerability to periodontal pathogens [33]. This implies that due to the already compromised immune response, the body's ability to combat even the simplest of bacterial pathogens, such as those in day to day activities of teeth brushing or use of dental floss, can infect the gingiva creating widespread hyperplastic infiltrates. On a much smaller scale, this phenomenon of gingival hyperplasia may also be seen in granulomatosis with polyangiitis (GPA), a disease characterized by systemic necrotizing vasculitis, marked by inflammation that typically involves the nose, lungs and kidneys. This relationship is evident in a case report published by Hanisch et al. (2017), where a patient with a history of GPA presented with a characteristic appearance of gingival swelling as one of the earliest signs of GPA recurrence [34]. While the major mechanism behind this pathology has not been widely explored as of yet, several other similar case reports have proposed that oral manifestations of hyperplastic gingiva may serve as early warning signs of either primary emergence or recurring GPA, modalities that may be useful in detecting a fatal disease course when the classic signs and symptoms are absent [35, 36, 37].

2.2. Histopathology and Molecular Biology

The main histological features of normal gingiva are keratinized stratified squamous epithelium, and the primary connective tissue surrounding the epithelium is the lamina propria, generally made of structures such as collagen fibers, extracellular matrix (ECM), and the vascular supply for the gingiva. The ECM contains collagen, elastin, proteoglycans, and non-collagenous structural glycoproteins (Radzki et al, 2024). The largest portion of the lamina propria is the gingival fibers which have collagen type I, III, and V, and the vasculature in the lamina propria contains collagen type IV. Overall, the fibers' main contribution is to maintain tone and structure for the tissue. The gingival fibers, mainly produced by fibroblasts, comprise oxytalan, eluanin, and elastin, which are the second fibrillar proteins found in healthy gingiva, and are also found within the subepithelial, medium, and deep layers of the gingival lamina propria in small amounts (Radzki et al, 2024). The histological features of gingival hyperplasia differ from regular gingival tissue in that gingival hyperplasia presents as epithelial hyperplasia or an increasing accumulation of ECM in gingival connective tissue–increasing the number of cells and/or fibrillar elements.

With gingival hyperplasia, there are inflammatory infiltrates present in both the epithelium and the lamina propria. Epithelium inflammation can be due to local irritation or local disease such as gingivitis. Păunică et al.

(2022) reported that the inflammatory cells present in the epithelium consisted exclusively of T-cells (CD3+ and CD5+), and no B-cells, plasma cells, or histiocytes [1]. In the setting of gingivitis, a local disease, there is a microbial plaque in the tissue which causes lymphocytic predominance. The lamina propria also consist of infiltrates of T-cells (CD3+ and CD5+) as well as many plasma cells (CD138+), a few histiocytes (CD68+), and very few B-cells (CD20+ and CD79a+) (Păunică et al, 2022). Because the lamina propria can go through deeper tissue levels than the epithelial layer, there is a more widespread inflammatory response in the connective tissue. Overall, there are multiple inflammatory pathways contributing to gingival overgrowth, as seen by the presence of the different classes of inflammatory cells. The inflammatory infiltrates in both epithelial and connective tissue are thought to be due to markers like IL-1, IL-6, and TNF-alpha (Li et al, 2013). The vascular changes present in gingival hyperplasia are seen most clearly through drug induced gingival hyperplasia as with phenytoin or cyclosporine. Uzel et al. (2001) state that Connective Tissue Growth Factor (CTGF) was present in significant quantities in phenytoin influenced tissue samples compared to normal gingival tissue samples [40]. CTGF has a context-dependent relationship with angiogenesis, acting to increase or decrease angiogenesis depending on the cellular environment or signaling pathway. In the context of Uzel et al's study, CTGF was inducing angiogenesis in drug-induced gingival hyperplasia by interacting with Vascular Endothelial Growth Factor- A (VEGF-A) and upregulating angiogenic factors, such as matrix metalloproteinases (MMPs).

Expanding on the etiopathogenesis of gingival hyperplasia, ECM degradation dysfunction plays a big role. Păunică et al. (2022) suggest that gingival hyperplasia can be due to the ECM being improperly degraded by collagenases. Building on this idea, Li et al. (2013) showed that gingival tissue-specific mesenchymal stem cells (GMSCs) exhibited increased proliferation in an in vivo inflammatory environment. This proliferation was followed by elevated expression of matrix metalloproteinases (MMP-1, MMP-2), proinflammatory cytokines (IL-1, IL-6, TNF-α), and type I collagen. All of this further explains how an inflammatory environment can impact the development of gingival hyperplasia by inducing fibrosis. When a pathologic process causes increased TGF-β expression, fibroblasts secrete more inflammatory cytokines which leads to tissue hyperplasia because of excess ECM production/decreased breakdown. However, that is not the only way gingival hyperplasia can present. Pharmaceutical-induced gingival hyperplasia and inflammatory gingival hyperplasia are both dependent on upregulating inflammatory cytokines and markers to promote dysregulated ECM deposition and growth. On the other hand, genetic influences in gingival hyperplasia occur through a slightly different pathway. One of the most commonly inherited forms of gingival hyperplasia is Hereditary Gingival Fibromatosis (HGF). Two genes (*SOS1* and *REST*) and four loci (2p22.1, 2p23.3-p22.3, 5q13-q22, and 11p15) have been known to have an association with HGF in a dominant inheritance pattern (Wu et al., 2022). Wu et al. (2022) more recently found a novel heterozygous missense mutation (c.2812G > A) in zinc finger protein 862 gene (*ZNF862*) which can play a role in increasing production of collagen alpha type 1(COL1A1), a profibrotic factor [41]. Depending on the gene mutations present in a patient, the degree of hyperplasia varies due to a combination of profibrotic factors and the induction of inflammatory pathway signaling.

One specific signaling pathway involved in gingival hyperplasia that is seen in inflammatory, pharmaceutical, and genetic etiologies is the TGF-β/SMAD1 signaling pathway. TGF-β induces phosphorylation of SMAD1 in fibroblast cells which causes a downstream signaling effect that leads to epithelial-to-mesenchymal transition (EMT) and anchorage-independent growth (Daly et al, 2008, Ramachandran et al, 2018). The overall downstream effects manifest as excess fibroblast production and ECM deposition. Roman-Malo et al (2019). further added on to the pathology of HGF in that an imbalance between reactive oxygen species (ROS) and antioxidant elements such as CoQ10 also contribute to the heterogenous presentation of HGF. Oxidative stress with limited antioxidant protection is what causes fibroblasts to increase collagen proliferation in gingival tissues. There are many different etiologies of gingival hyperplasia– whether they be pharmaceutical, inflammatory, or genetic–and the management of each cause ultimately depends on the etiology. However, what is similar among all etiologies is that there is either direct hyperplasia of epithelial tissue due to local inflammation or there is an increase in the deeper levels of ECM via processes that incite excess collagen deposition or angiogenesis of vasculature. Because of the complex manifestations of gingival hyperplasia, there may

be multiple processes involved in the manifestation of the disease

2.3. Clinical Presentation and Diagnosis

Despite the numerous etiologies, gingival hyperplasia can be broadly characterized as taking on localized or generalized forms. Localized forms refers to involvement of a specific area of the oral mucosa, including a few teeth or quadrant of the mouth [45]. Such forms of localized gingival hyperplasia commonly arise from external trauma to the region or local irritants. Underlying causes include pyogenic granulomas, localized juvenile spongiotic gingival hyperplasia (LJSGH), and vitamin C deficiency (scurvy) [46, 47]. Generalized forms of gingival hyperplasia include widespread involvement affecting multiple areas. Drug-induced gingival hyperplasia, hereditary gingival fibromatosis, and hormonal etiologies commonly present as generalized gingival hyperplasia [48]. Generalized forms commonly affect significant portions of the teeth and may include extra-oral manifestations including asymmetric macrocheilia and mouth breathing [49]. By recognizing localized and generalized patterns of change, clinicians can better differentiate underlying causes.

Despite these several different etiologies, there are many common histological patterns that are typically observed in patients with gingival hyperplasia. Many etiologies of gingival hyperplasia commonly present with characteristic changes in the epithelium such as hyperplasia, acanthosis, and papillomatosis [1]. Such changes are commonly present in histology with focal vascular dilation. Other common histologic findings include changes in connective tissue such as a marked increase in fibroblast density [1, 50] and alterations in the collagen synthesis pathway causing excessive deposition [51]. Certain hematologic causes of gingival hyperplasia, such as different leukemias, have been associated with leukemic infiltration manifesting as numerous lymphocytes and monocytes within the area [1]. Such histologic patterns can vary in intensity between patients, warranting a system to quantify this change.

There have been a number of different grading indices created to score gingival hyperplasia. Of these indices, the most accurate and reliable grading system is the C Index [52]. This system grades gingival hyperplasia using intraoral photographs on a score from 0-3 based on numerous factors, including the structural extent of the enlargement, the area of tooth surface that is covered, the thickness of the hyperplasia, and many other factors. Other indices, such as the first index created by Angelopoulos and Goaz in 1972, have also been found to be applicable in different circumstances, but the C index has been found to be the most statistically reliable [52]. Grading systems allow clinicians to better understand the extent of the disease, while understanding symptoms and specific presentation is equally important for comprehensive evaluation.

Gingival hyperplasia can arise with a number of associated symptoms. Patients may commonly experience swollen or bleeding gums, oral ulcerations, pain or tenderness, or halitosis due to plaque buildup [53]. In certain cases, gingival hyperplasia can interfere with mastication and speech, causing an overall poor quality of life in these patients [54]. Beyond the plethora of associated symptoms that commonly arise with this condition, there are also a number of complications to look out for. Different etiologies of gingival hyperplasia are associated with different complications. Drug-induced causes, such as from calcium channel blockers or anticonvulsants, can result in an increased number of dental caries and decalcification of detention [55]. Gingival hyperplasia caused by neurofibromatosis can result in complications such as mental handicapping, development of speech impediments, and other neurologic manifestations such as headaches, seizures, and psychological disorders [55]. Together, these symptoms and complications underscore the importance of early detection.

Because of the number of etiologies that can manifest with gingival enlargement, a thorough clinical examination is necessary when diagnosing patients with this presentation. A number of clinical examination techniques must be employed during examination. During the beginning of the patient encounter, it is crucial to acquire a detailed familial, medical, and drug history from the patient as these may provide valuable information in the development of a diagnosis [56]. Visual examination and palpation can reveal the overall color and texture of the lesions, as well as whether there is any tenderness or fibrosis. Further examination can include techniques such as radiographic imaging and biopsy to give the medical team information regarding the underlying pathology involved in the development of the gingival enlargement. Such techniques can provide clinicians with all the necessary information to support a diagnosis of the underlying etiology. Radiographic techniques commonly used in patients with gingival hyperplasia

include projection radiography, cone beam CT, and MRI. On radiographic imaging, patients with gingival hyperplasia can commonly present with gingival pockets or pseudopockets that arise from deepened gingival sulcus around teeth at the gingival margin [57]. Beyond this, gingival hyperplasia is also commonly associated with bone loss or displacement of teeth that can be visualized on orthopantomogram and intraoral periapical radiographs [58]. The teeth displacement seen in patients with gingival hyperplasia is said to give a "floating-tooth" appearance and requires surgical intervention [59]. Other radiographic findings that are commonly found in systemic conditions, such as leukemia, include alveolar and periodontal bone loss, loss of lamina dura, increased radiolucency in some teeth [60].

The differential diagnosis of gingival hyperplasia encompasses a wide spectrum of localized and systemic conditions, necessitating a detailed approach to identifying the underlying cause. Hyperplastic gingivitis and periodontitis are inflammatory conditions that are characterized by edema, granulation tissue formation, and fibrosis that contribute to gingival enlargement [61]. Some of the other causes of gingival enlargement include secondary causes to underlying systemic diseases such as leukemia, Crohn's disease, sarcoidosis, tuberculosis, and Wegener's granulomatosis [62]. Each of these underlying systemic conditions can cause a secondary gingival enlargement with their own unique histologic and radiographic features and are therefore important to rule out in the differential. Other etiologies of gingival enlargement can also be caused by a number of genetic disorders that can be ruled from a differential through examination of family history and genetic testing [62]. Gingival enlargement can also be a manifestation of hormonal changes during pregnancy or puberty or vitamin C deficiency [62]. There are a number of differentials to consider in the diagnosis of gingival hyperplasia and it is therefore critical that a thorough clinical examination, detailed patient history, and appropriate diagnostic techniques be applied in the assessment of these patients.

2.4. Management Strategies

2.4.1. Non-surgical approaches

Dental plaque can be both a cause and consequence of gingival hyperplasia. Effective plaque control is essential in managing gingival hyperplasia, as it reduces local inflammation and prevents progression regardless of etiology [63]. Mechanical debridement through professional cleanings and reinforcement of proper oral hygiene techniques including twice-daily brushing, interdental cleaning, and antimicrobial mouth rinses, can reduce local inflammatory stimuli that exacerbate gingival overgrowth. Patients should be taught the Bass brushing technique, which uses gentle vibratory motions at a 45-degree angle to the gumline, with adjustments made based on the extent of gingival enlargement [64]. Extra-soft toothbrushes are recommended to minimize tissue trauma, especially in areas with lobulated or overlapping gingiva. Electric and sonic toothbrushes offer enhanced plaque removal, particularly interproximally, and can improve patient compliance. Daily flossing is also critical but must be performed carefully to avoid lacerations or bleeding, especially in immunocompromised individuals.

Drug substitution is a cornerstone of managing drug-induced gingival overgrowth, particularly when conservative measures alone are insufficient. The most commonly implicated drug classes include anticonvulsants (e.g., phenytoin), immunosuppressants (e.g., cyclosporine), and calcium channel blockers (e.g., nifedipine and amlodipine) [65,66]. Discontinuing or replacing the offending agent can significantly reduce gingival overgrowth. Alternatives with a lower risk of DIGO include carbamazepine or valproic acid in place of phenytoin, and diltiazem or verapamil instead of nifedipine [8]. Cyclosporine presents a greater challenge due to fewer substitution options, though tacrolimus has demonstrated reduced gingival side effects. Additionally, adjunctive use of azithromycin with cyclosporine has been associated with a decrease in the severity of gingival enlargement [67]. Mechanistically, azithromycin inhibits the proliferation of gingival fibroblasts and reduces collagen production. It also restores the activity of matrix metalloproteinases 1 and 2, enzymes that help regulate collagen breakdown, thus mitigating fibrotic tissue buildup. Ultimately, all medication changes should be coordinated with the prescribing physician to maintain systemic disease control while minimizing oral side effects. A collaborative, patient-specific approach is essential to balance medical needs with oral health outcomes. Following initial treatment, long-term maintenance is critical in preventing recurrence. Regular dental visits, reinforcement of oral hygiene, and periodic re-

evaluation of systemic medications or underlying conditions are necessary components of ongoing care. Patient education remains central to sustaining therapeutic gains.

2.4.2. Surgical interventions

When gingival overgrowth significantly impacts quality of life, surgical interventions are considered. Gingivectomy remains the primary surgical approach for managing moderate to severe cases of gingival hyperplasia, particularly when non-surgical therapies fail to control the overgrowth or when functional and aesthetic concerns arise [8]. Indications for gingivectomy include persistent pseudopocket formation, interference with mastication or oral hygiene, speech impairment, and patient discomfort due to tissue overgrowth. The decision to proceed with surgical intervention depends on the extent of enlargement, underlying etiology, and overall periodontal health. The conventional scalpel-based gingivectomy involves external bevel incisions to excise excess gingival tissue, followed by contouring to re-establish physiologic architecture [68]. This technique offers precision and predictable outcomes, especially in cases of fibrotic or drug-induced gingival overgrowth. However, it may be associated with intraoperative bleeding, postoperative discomfort, and slower healing times.

Periodontal flap surgery is recommended in cases involving extensive gingival overgrowth affecting more than six teeth, or when gingival enlargement is accompanied by attachment loss and underlying osseous defects [69]. This procedure involves direct access to the underlying tooth roots and alveolar bone. Additionally, flap procedures are preferred when conventional gingivectomy would risk complete removal of keratinized tissue, potentially leading to mucogingival complications. For shorter recovery and decreased recurrence rates, laser excision is indicated. Laser-assisted gingivectomy has become a valuable alternative to conventional scalpel-based techniques, particularly for patients with systemic contraindications to traditional surgery or those seeking improved comfort and aesthetic outcomes [70]. Laser procedures offer several clinical advantages, including enhanced precision during tissue excision, reduced postoperative pain and analgesic requirements, minimal inflammation, effective hemostasis, and suture-free healing [71]. However, these benefits must be weighed against limitations such as higher equipment costs and longer procedural times. Commonly utilized laser systems in the management of gingival overgrowth include carbon dioxide (CO_2), diode, neodymium-doped yttrium aluminum garnet (Nd:YAG), and erbium-doped yttrium aluminum garnet (Er:YAG) lasers.

Recurrence of drug-induced gingival enlargement is a well-documented concern following surgical treatment [72]. Meticulous home care and professional cleanings can decrease the rate at which recurrence occurs. While recurrence can occur as early as 3 to 6 months post-surgery, most patients maintain surgical outcomes for at least 12 months. One study comparing gingivectomy and periodontal flap surgery for cyclosporine-induced gingival overgrowth found that periodontal flap procedures were associated with a slower return of increased pocket depth at the 6-month follow-up [73].

2.4.3. Emerging Therapies

Recent advances in molecular biology have identified key signaling pathways involved in the pathogenesis of gingival overgrowth, including TGF-β, CTGF, and NF-κB [74]. Targeting these pathways may suppress fibroblast proliferation and extracellular matrix deposition. Preclinical studies have shown that selective inhibition of these molecular drivers can reduce fibrotic tissue formation, offering the potential for non-surgical disease control [72, 75]. Cytokines play a central role in the pathogenesis of gingival overgrowth, particularly in drug-induced cases. Elevated levels of interleukin-1 (IL-1) and interleukin-6 (IL-6) have been consistently observed in overgrown gingival tissues, where they contribute to chronic inflammation, fibroblast proliferation, and extracellular matrix accumulation [76]. These pro-inflammatory cytokines act synergistically with growth factors to perpetuate the fibrotic response and disrupt normal tissue homeostasis.

Given their upregulation in affected tissues, IL-1 and IL-6 represent promising targets for therapeutic intervention [77]. Modulating these cytokine pathways through anti-inflammatory agents or biologics may reduce inflammation, slow or reverse fibrotic changes, and prevent the progression of gingival enlargement. Early periodontal intervention aimed at reducing cytokine expression may not only alleviate active inflammation but also serve as a preventative measure against recurrence in high-risk patients. As research continues to clarify the cytokine signatures specific to different etiologies of

gingival hyperplasia, more targeted, non-surgical treatment strategies may become viable.

Systemic antifibrotic agents such as pirfenidone and nintedanib, originally developed for idiopathic pulmonary fibrosis, are being explored for their potential use in gingival hyperplasia. Pirfenidone has demonstrated broad antifibrotic activity in preclinical models by reducing fibroblast proliferation, collagen synthesis, and modulating key mediators like TGF-β, PDGF, and TNF-α [78]. Similarly, nintedanib, a multi-receptor tyrosine kinase inhibitor targeting PDGFR, FGFR, and VEGFR, has shown promise in preventing and reversing tissue fibrosis in both pulmonary and nonpulmonary models [79]. While clinical data in oral tissues remain limited, these agents offer a mechanistic rationale for repurposing in localized gingival applications, particularly for patients at high risk of recurrence. Additional candidates such as rapamycin analogs, which suppress fibroblast activation via mTOR inhibition, further expand the therapeutic landscape. Although challenges such as off-target effects and limited human data persist, these antifibrotic pharmacologics represent a promising direction for non-surgical, biologically targeted management of gingival fibrosis.

Given the diverse etiologies of gingival hyperplasia, ranging from drug-induced to genetic and inflammatory causes, personalized treatment strategies are essential. For example, patients with phenytoin-induced overgrowth may respond better to drug substitution and antifibrotic agents, while those with inherited gingival fibromatosis may benefit from early surgical intervention followed by gene-targeted therapies in the future. Integrating genetic, pharmacologic, and inflammatory profiles into treatment planning may optimize outcomes and reduce recurrence.

2.5. Current Limitations in Treatment Approaches

Despite advancements in both surgical and non surgical management of gingival hyperplasia, current treatment mainly caters to symptomatic control and lacks the ability to address underlying molecular issues (Tungare et al., 2022). While non- surgical therapies such as plaque control and drug substitution could be effective in mild cases, they do not offer long term disease modification and rely heavily on patient compliance (Thompson et al., 2004). While drug substitutions can be effective in drug induced cases, options remain restricted nonetheless, especially with agents such as cyclosporine (Bharti et al., 2013). Surgical interventions such as gingivectomy and flap procedures could restore function and aesthetics, however have high recurrence rates within 6-12 months post treatment, especially in drug induced forms (Camargo et al., 2001). These shortcomings point to a large gap in therapeutic strategies failing to target the root pathophysiology of fibrotic gingival enlargement. Recent advances have revealed numerous distinct pathways, such as TGF-B/SMAD signaling, CTGF overexpression, and IL-1/IL-6 driven inflammation as key mediators of persistent tissue overgrowth (Bharti et al., 2013; Kim et al., 2008). It is vital to investigate each pathway's molecular distinctions in order to create precise targeted therapy. Novel emerging antifibrotic agents such as pirfenidone and nintedanib, and mTOR inhibitors such as rapamycin analogs may hold great potential, however are still experimental in oral applications (Kim et al., 2008). There is also a growing requirement to incorporate genetic screening and transcriptomic profiling into clinical decision making, in order to identify patients at a higher risk of recurrence or a potential poor response to existing therapies (Tungare et al., 2022). Though current treatments target symptom management, the increasing studies on molecular targets warrants a shift toward local molecular modulators for long-term control and improved patient outcomes.

3. CONCLUSION

Gingival hyperplasia arises from a convergence of dysregulated fibroblast activity, aberrant extracellular matrix turnover, pro-fibrotic signaling such as TGF-β/SMAD and CTGF pathways, chronic inflammation, and genetic predispositions. Understanding the key pathogenesis behind gingival hyperplasia starts with the recognition of ECM degradation dysfunction. Molecular targets can vary between etiologies ranging from targeting matrix metalloproteinases, modulating cytokines IL-1/IL-6, or through addressing genetic mutations such as ZNF862 affecting fibroblast and collagen type I proliferation. By understanding the significance of such pathways, therapies can become more etiology specific. Such an approach holds promise for reducing recurrence and improving patient outcomes long-term.

The clinical manifestations of gingival hyperplasia can also vary with the etiology, whether drug-induced, hereditary, inflammatory, hormonal, or systemic. Recognizing these underlying causes is key to tailoring

interventions, from targeted plaque control and medication modification to emerging antifibrotic or cytokine-targeted therapies, and careful determination of when surgical intervention via gingivectomy is warranted. Complex presentations of gingival hyperplasia include overlap with systemic conditions and demand a multidisciplinary approach that leverages dental, medical, and, where appropriate, genetic expertise. Creating such multidisciplinary maintenance protocols that integrate oral hygiene reinforcement with dermatologic care is important for functional and aesthetic outcomes for patients. Future studies are necessary to evaluate the safety, efficacy, and optimal delivery of emerging molecular modulators for long-term management of gingival hyperplasia.

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