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Gingival Hyperplasia: A Collateral Damage Due to Various Drugs

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ABSTRACT

Gingival hyperplasia or gingival enlargement is abnormal overgrowth of gingiva around the teeth, arising most likely as a side effect of conventional medications for controlling seizures, high blood pressure, immunosuppressants often referred as Drug Induced Gingival Hyperplasia (DIGH). It causes swelling, bleeding, difficulty with chewing and pronunciation. Long-term use of these drugs has been linked to overexpression of several chemokines and interleukins, causing gingival overgrowth as an aftereffect. It is still largely unknown how the fibroblasts proliferate during the period of drug administration and what kind of morphological changes occur when the drug accumulates in the cell cytoplasm. This paper reviews the current literature surrounding the various drugs and their impact on gingival enlargement that in turn affects the oral hygiene of patients receiving the medications and ways to rectify the damage.

Introduction

Abnormal proliferation of gingiva is termed gingival hyperplasia. It results in increased pocket depth caused by an increase in the height of the gingiva and not an attachment loss. The resultant pseudo-pocket can accumulate plaque, which if untreated, may progress to attachment loss [1,2]. Proper management of the hyperplasia relies on the accurate diagnosis of the etiology leading to the enlargement. Several factors, such as age, gingival inflammation, genetic predisposition influence the occurrence of gingival hyperplasia. Based on etiological factors, hyperplasia can be due to continuous irritation or inflammation, prolonged usage of drugs (anti-seizure, anti- hypertensive, auto immune) or due to neoplastic oral conditions. Relative, pseudo or false pockets exist when there is gingival enlargement without destruction of periodontal tissues [3]. DIGH is dose dependent and is reported to be reversible. In certain circumstances, where the complete cessation of the drugs cannot be accomplished, it has been seen that addendum therapy with certain antibiotics can reverse the gingival damage [4].

DIGH usually develops after a period of one to three months of starting the drug. The excess accumulation of collagen in connective tissue has been histologically revealed. The gingival fibroblasts are activated that secrete excess collagen, resulting in hyperplasia. Certain types of drugs do not cause increased production of collagen, however they are known to lower the rate of degradation.

Role of Cytokines

"Cytokine" has its derivation from two Greek words "cyto" meaning cell and "kinos" meaning movement. Hence, cytokines are described as "immunomodulating agents," or agents that modulate or alter the immune system response. Cytokines, including interleukins 1–10, tumor necrosis factor alpha (TNF-alpha), and interferon gamma (INF-gamma) are produced predominantly by macrophages and lymphocytes but can be synthesized by other cell types as well. Their role in inflammation is complex. They act through cell surface receptors

and are especially important in the immune system [5]. These polypeptides modulate the activity and function of other cells to coordinate and control the inflammatory response. IL-1, IL-6, and TNF-alpha mediate the acute phase response and pyrexia that may accompany infection and can induce systemic clinical signs. In the acute phase response, interleukins stimulate the liver to synthesize acute-phase proteins, including complement components, coagulation factors, protease inhibitors, and metal-binding proteins. By increasing intracellular Ca2+ concentrations in leukocytes, cytokines are also important in the induction of PLA2 [6]. Colony-stimulating factors are cytokines that promote expansion of neutrophil, eosinophil, and macrophage in the gingival tissue. In chronic inflammation, cytokines IL-1, IL-6, and TNF-alpha contribute to the activation of fibroblasts and osteoblasts and to the release of enzymes such as collagenase that can cause cartilage and bone resorption. Fibroblasts are the main type of cells of the connective tissue. Following tissue injury, the nearby fibroblasts proliferate and secrete tropocollagen (precursor of collagen) and migrate into the wound to produce large amounts of collagenous matrix, which facilitates the healing process. Cytokines are essential protein-based regulators of immune responses, and any abnormality in their signaling pathways can lead to various diseases, including autoimmune conditions.

Table 1. Gingival enlargement associated with different drugs:

Anti-seizure	Levetiracetam	Phenobarbital	Diphenylhydantoin
Anti-hypertensive	Amlodipine	Nifedipine	
Immuno-suppressive	Cyclosporine-A	Tacrolimus	

Anti-Seizure Medication Induced GH

Levetiracetam

Levetiracetam is used as a first line treatment for focal and generalized seizures. It has least interactions with other drugs and has been safely used in pregnant, hepatic disease and patients with coagulopathies. Levetiracetam is well absorbed orally with or without food and is eliminated by metabolism (plasma and liver) and renal excretion. The anticonvulsant mechanism of action of levetiracetam appears to reflect interference with the release of synaptic vesicle contents. Because of its short half-life, caution is recommended to avoid abrupt discontinuation. Most common adverse effects that have been reported include fatigue, somnolence, irritability, aggression, asthenia, dizziness, infection, nausea, anorexia, blurred vision [7]. A rare adverse event with usage of levetiracetam that was recently reported was on a patient that developed gingival hyperplasia. Five days after starting the medication, the patient exhibited signs of painful oral ulcers and swollen gums. There was no prior history of compromised oral health at the time of examination before prescribing Levetiracetam. The medication was stopped and on follow-up after a month the gum hypertrophy was completely resolved [8].

Diphenylhydantoin

Phenytoin is used as a first line of treatment for temporal lobe, tonic-clonic, and psychomotor seizures. It has been used as the most common adjuvant anticonvulsant in refractory epilepsy. Phenytoin is metabolized largely by the hepatic cytochrome P450 enzyme system to inactive metabolites. It is 90% bound to serum albumin. Phenytoin is involved in several drug interactions [9]. Phenytoin has been associated with liver disease. Because

of its short half-life, abrupt discontinuation is avoided. Local tissue injury and necrosis can occur with or without extravasation of phenytoin. In the body it gets metabolized to 5-(4-hydroxyphenyl) 5-phenyl hydantoin (4-HPPH), responsible for overgrown gingival tissue. Phenytoin alkalinity plays an important role in the onset of this side effect [10]. Recent study conducted on fibroblasts that were challenged in-vitro with various concentrations of phenytoin showed an elevation in the deposition of the extracellular matrix. Fibroblasts hyperproliferation in connective tissue with the deposition of extracellular matrix was increased multifold. Cell proliferation along with epithelial–mesenchymal transition, resulting in changes in the expression of adhesion molecules. Folic acid supplementation has been found to slow down the incidence of GH in children receiving phenytoin as a monotherapy to control epilepsy for 6 months [11].

Immunosuppressive Medication Induced GH

Cyclosporin-A

Cyclosporin-A is an immunosuppressant and is widely administered in case of organ transplantation to prevent acute or chronic rejection in patients with autoimmune diseases. It is also used for treatment of certain autoimmune conditions such as rheumatoid arthritis, keratoconjunctivitis sicca, myasthenia gravis, pemphigus foliaceus, chronic-active hepatitis, and immune mediated hemolytic anemia [12]. Cyclosporine primarily acts through direct inhibition of T-cell function, cell-mediated immunity, including T-helper cells and T-cytotoxic lymphocytes, and indirect effects on humoral immunity. It increases the gingival tissue volume by a connective tissue response, characterized by excessive accumulation of extracellular matrix proteins. It has been demonstrated that cyclosporin exhibits high inflammation with low fibrosis by targeting cyclophilin and inhibiting T-cell production of interleukin 2 and provides anti-fibrotic effect on collagen biosynthesis and accumulation [13]. The effect of cyclosporine on gingival fibroblasts is dose dependent. Long-term exposure with low dose was seen to not have influence on the proliferation of fibroblasts, however a high dose leads to high expression of interleukin 6 which in turn causes increased synthesis of collagen and aminoglycan deposition.

Anti-Hypertensive Drug Induced GH

Amlodipine

Systemic arterial hypertension is commonly reported in middle-aged-to-older human beings. Amlodipine is recommended as the initial antihypertensive drug. In 1994, the first case of GH induced by amlodipine was reported [14]. Hypertrophy in patients receiving 10 mg of amlodipine daily within 2 months of the onset of treatment was seen [15]. Amlodipine belongs to the category of calcium channel blockers. They inhibit of calcium ion influx in cardiac and smooth muscle cells resulting in coronary and peripheral arterial vasodilation, reduced heart rate, decreased myocardial contractility and oxygen utilization by the myocardium. The reduced calcium uptake interferes with collagenase which in turn stimulates gingival fibroblast proliferation. interferes with collagen synthesis [16].

Current Treatments

Cold Surgery

Gingival resection, also termed as gingivectomy, is focused on removing deposits and diseased tissue and re-gaining attachment with preservation of at least 2 mm of attached gingiva [17]. There are different techniques available using cold steel, diamond burrs or electro surgery. Initially, the incision line must be calculated to achieve a new free gingival margin approximately 1–2 mm coronally to the cement-enamel junction. As plaque may interfere with wound healing, careful but disciplined home care is recommended, and tooth brushing is started as early as 14 days post-surgery. Gingivectomy is a coronally directed, externally beveled incision, used primarily for the removal of gingiva when no underlying osseous lesions are present [18]. An adequate band of attached gingiva must be there both pre-operatively and post-operatively to protect the teeth. Although gingivectomy may eliminate the supra bony pocket, heating time of exposed tissue is longer. Gingivoplasty is often performed to remove any uneven areas and to accomplish final contouring of the gingiva. A gingivectomy is contraindicated when there is inadequate attached gingiva, or horizontal and vertical pockets extend below the mucogingival line. Cold steel incision is a cheap and accessible method. However, considerable intraoperative bleeding results, thus limiting the surgical field view and requiring frequent swabbing. Cold blades dull quickly.

Laser Surgery

Diode lasers are best absorbed by melanin and hemoglobin present in gingival tissues. Hemostasis is achieved while performing the gingivectomy. The Co2 laser is versatile for precise incising or vaporizing the gingiva. Higher CO2 laser power is used to remove moderate amounts of hyperplastic gingiva. For thicker areas, CO2 laser is used in diverging mode for coagulation to help control bleeding after scalpel blade gingivectomy. A clean, nice cut offers a clear view of the surgical field. Working time is also noticeably shorter. For the fastest, most comfortable, and lowest recurrence rate, the use of 450 nm laser is most efficient [19]. It involves minimum tissue necrosis. Laser surgery is an amazing way to do surgery. The ability to change spot size, pulse mode, and depth of incision is extremely accurate. Pressure on the scalpel affects the incision, but with the laser no pressure is applied, and no tissue distortion is present during the incision. Local tissue damage is at a minimum compared with electrocautery and healing is rapid. Pain is lessened due to the way the laser cuts the nerve tissue. Hemostasis is also very effective in giving the surgeon an unimpaired surgical field.

In all cases, trimming away excess gingiva and restoring a normal sulcus depth (3 mm) permits removal of periodontal disease as an inciting or contributory cause to the gingival enlargement [20]. Whenever patients are on life-saving medications or if the patient is determined to have a genetic predisposition, counseling is necessary so that repeat treatments will be most likely.

Discussion

This review attempts to highlight the various medications and the mechanisms by which gingival hyperplasia happens. An important aspect to keep under consideration is that the damage is reversible in many cases since it is dose dependent. Multiple factors, such as age, genetic predisposition, and presence of gingival inflammation, play a vital role in the occurrence of this condition. In addition to being unaesthetic and uncomfortable, overgrowth leads to accumulation of microorganisms causing oral infections which in turn affects the overall well-being of the patients. With newer and effective management approaches, the possibility of complications can be easily minimized.

Conclusions and Implications

Prolonged and high dosage use of anticonvulsants, anti-hypertensive and auto-immune drugs increase the risk of gingival hyperplasia. The impact on fibroblastic proliferation is exacerbated with exposure time to these medications. The understanding of gingival proliferation pathogenesis is still largely unknown and inadequately studied. The simplest and least invasive treatment would be alternative medication that does not have this side effect. It would be interesting to navigate the possibilities of polypharmacy with these medications, so that their dosage can be reduced to minimize hyperplasia, while maintaining the patient's response to treatment.

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