Drug Related Gingival Hyperplasia
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Pathology-Thurs 10 AM
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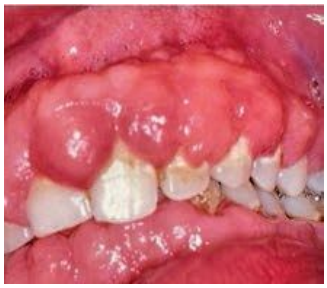
Overview

Gingival hyperplasia describes a periodontal condition where the tissue of the gum becomes inflamed and enlarged. Hyperplasia specifically refers to an increase in the number of cells, so in gingival hyperplasia, there is an increase in the amount of gingival cells due to swelling. Side effects are bleeding as well as problems with chewing. esthetics and pronunciation. In more severe cases, it can also cause tooth mobility and detachment due to bone resorption (Hatahira 2). All of these symptoms can cause a deterioration in the quality of the patient's life. Although there are many cases of gingival enlargement, drug induced gingival hyperplasia, the primary focus of our discussion, is caused by the influx of certain medications.



DIGH as seen in a teenager

Etiology

More than 20 drugs are associated with drug induced gingival hyperplasia (DIGH). These drugs are all taken for nondental purposes and can be divided into three different subclasses: anticonvulsants, calcium channel blockers and immunosuppressants (Hatahira 1). Anticonvulsants, such as phenytoin, phenobarbital, lamotrigine, vigabatrin, ethosuximide, topiramate and primidone are usually taken to treat epileptic seizures and bipolar disorder. They have an average onset rate of 37 days from the starting of the drug to having visibly noticeable symptoms of hyperplasia (Hatahira 5). Calcium channel blockers, such as nifedipine, amlodipine, and verapamil, are taken for the treatment of hypertension. They have an average onset rate of 262 days before gingival enlargement becomes clinically visible. Lastly, immunosuppressants, such as cyclosporine, taken as a treatment for autoimmune diseases, have an average onset rate of 71 days (Hatahira 5)

Despite their pharmacological diversity, the three major drug classes causing gingival overgrowth have a similar mechanism of action at the cellular level, where they inhibit intracellular calcium ion influx. This changes the ongoing metabolism of connective tissue fibroblasts, causing an increase in the amount of extracellular matrix. This starts a biochemical cascade where "the inflammatory response is further provoked, large amounts of inflammatory protein are produced, and the oral epithelium is thickened, resulting in a clinically visible gingival enlargement" (Bharti 173)

It should also be noted that although DIGH is primarily related to drug dosage, it can further be accelerated by gingival inflammation caused by dental plaque. In a study of amlodipine induced gingival hyperplasia, researchers found the higher the plaque score for the patient, the more severe was the case of hyperplasia. In fact, in patients with good oral hygiene who had been long term users of the drug amlodipine, no gingival changes were seen (Tejnani 228). This goes to show us that there is a variable gingival response in patients taking drugs. Several factors such as age, genetic predisposition, presence of preexisting plaque, and gingival inflammation can influence the relationship between the drugs and gingival tissue (Bharti 172).

TABLE 1: Most Commonly Prescribed Drugs Associated with Gingival Enlargement

Category	Generic Drug	Brand Names
• Anticonvulsants	• Phenytoin	• Dilantin
	• Valproic acid	• Depakene
	• Carbamazepine	• Tegretol
	• Vigabatrin	• Sabril
• Calcium channel blockers	• Amlodipine	• Norvasc
	• Diltiazem	• Cardizem, Cartia, Dilacor, Taztia, Tiazac
	• Felodipine	• Plendil
	• Isradipine	• DynaCirc
	• Nicardipine	• Cardene
	• Nifedipine	• Adalat, Nifedical, Procardia
	• Nisoldipine	• Sular
	• Verapamil	• Calan, Covera-HS, Verelan
• Immunosuppressants	• Cyclosporine A	• Neoral, Sandimmune
	• Tacrolimus	• Prograf
	• Mycophenolate mophetil	• CellCept
	• Sirolimus	• Rapamunel

Demographics

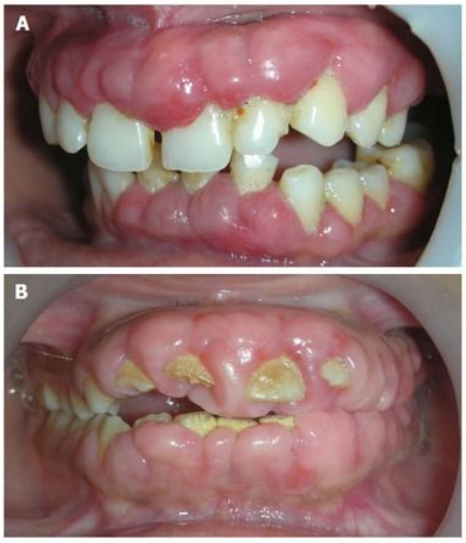
As previously discussed, since biofilm is a risk factor for all periodontal disease, those with a higher plaque index are at increased risk of developing drug related gingival enlargement due to the harmful bacteria already present in the mouth. Though one would assume it would be more frequently found in the older generation who rely on medications, children and teenagers are actually at higher risk of developing the gingival enlargement from cyclosporine and phenytoin. The lesions are also more commonly found in men than women with a ratio of 3:1. Dosage of the medication, however, does not seem to affect the likelihood of one developing the condition (Livada 8)

Clinical Presentation

It usually takes 1-3 months for the clinical symptoms of DIGH to develop. “The growth starts as a painless, beadlike enlargement of the interdental papilla, extending to the facial and lingual gingival margins. When uncomplicated by inflammation; the lesion is mulberry-shaped, firm, pale pink, and resilient; with a minutely lobulated surface and no tendency to bleed” (Bharti 174).

As the disease progresses, the marginal and papillary enlargements may fuse and develop into a massive tissue fold covering much of the enamel surface. At this stage, secondary inflammation manifests and the enlargement produces a red or bluish red discoloration, obliterates the lobulated surface demarcations, and shows increased bleeding tendency (Bharti 3). Inflammation now exceeds to the point that oral self care becomes difficult.

The enlargement is usually seen throughout the mouth, but is more severe in the maxillary and mandibular anterior regions. It occurs in area in which teeth are present, not in edentulous spaces, and the enlargement disappears in areas from which teeth are extracted.



Pic A shows an early manifestation of DIGH while pic B depicts a later stage

As the condition worsens, the patient may experience bleeding, pain, tissue friability, abnormal movement of the teeth, changes in phonetics and occlusion as well as the appearance of dental caries and periodontal disease (Ahmed 213). More severe destruction of the periodontium and bone is specially more likely if the periodontal infection is not treated in time.

Biopsy/Histology/Radiographic Features

Drug induced hyperplasia is associated with a thickening of epithelium, with elongated rete pegs and fibrosis in the lamina propria. “There is an increased number of fibroblasts containing large amounts of mucopolysaccharide sulphate in addition to an overall increase in tissue volume. The thickness of the oral epithelium is generally 5-10 times thicker in DIGH versus controls” (Ahmed 213).

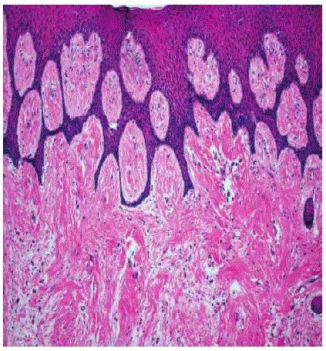


Figure 4: Photomicrograph of HGF tissues shows a dense connective tissue predominantly consisting of thick and irregularly arranged collagen fibers underlying an epithelium with elongated rete pegs (hematoxylin and eosin stain; original magnification X100).

Additionally, interleukins, proinflammatory cytokines that are elevated in inflamed gingival tissues, are also found in large quantities in DIHG. IL-1β, IL-6, both of whom “may play a role in the fibrogenic responses of the gingiva to these medications, are specific biochemical markers to look for” (Bharti 174). Histologically, there are also significantly higher numbers of basement membrane discontinuities in overgrowth tissues, sometimes containing epithelial-like cells. The disrupted basal membrane structure will be “accompanied by a discontinuous collagen type IV expression pattern” in gingival hyperplastic tissues (Bharti 174).

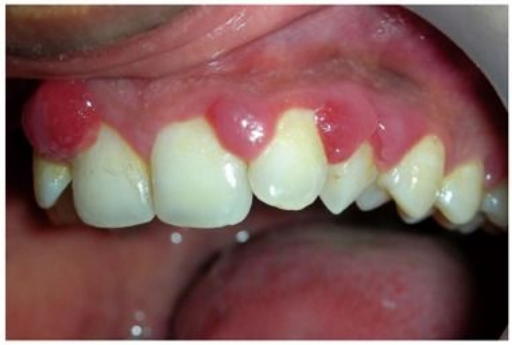
When a patient presents with enlarged gingiva, one must take radiographs to differentiate the condition from bone diseases and tumors. If the dental x rays show an increase in size of underlying osseous tissue, the cause may be tori, exostosis, Paget’s disease, cherubism or osteoma. Whereas, if the radiographs show bone with horizontal and vertical loss in dimension characteristic of periodontal disease, DIGH may be the underlying cause. In this case, a biopsy and a microscopic examination are ordered. If the biopsy shows fibrotic tissue with an abundance of fibroblasts and collagen fibers, DIGH may be the cause. In such a case, it is best to consult the patient’s physician, requesting him to substitute/stop one suspicious drug that may be causing the enlargement at a time, starting with the one that would have least effect on patient’s routine schedule (Agrawal 782).

Differential diagnosis

There are many other conditions that may be mistaken for drug induced gingival hyperplasia. If the drug induced gingival inflammation is localized or restricted to a certain area, which it may be in the early stages, it may be mistaken for peripheral fibroma, pyogenic granuloma, peripheral giant cell granuloma, gingival cysts or benign/malignant neoplasms (Agrawal 780-81). The presence of a neoplasm will likely be assumed if the enlargement appears “as a slowly growing spherical mass that tends to be firm and nodular, with a wart-like protuberance from gingival surface” (Bharti 177).

Conversely, if the gingiva appears to be generally enlarged, the condition may be mistaken for inflammatory gingival enlargement, conditional/hormonal gingival enlargement, or perhaps even systemic disease based gingival enlargement (Agrawal 782-86). Because inflammatory gingival enlargements, caused by physical irritants such as microbial deposits or

overhanging restorations, often appear as deep red or bluish red swellings with a friable smooth shiny surface, they may be mistaken for DIGH of a later stage (mixed with secondary inflammation). Similarly, conditional gingival enlargements, such as those caused by pregnancy, a Vitamin C deficiency or plasma cell gingivitis, also show inflammation of papillary gingiva, and thus can also be reasonably mistaken as DIGH. Certain systemic diseases such as leukemia, sarcoidosis, tuberculosis, and other granulomatous diseases can also result in gingival enlargement. However, hematological tests, such as in leukemia, and histopathological examination, such as in sarcoidosis or tuberculosis, are useful in establishing the diagnosis (Bharti 177).



Pregnancy infused gingivitis may be confused for DIGH

Treatment

Currently there are surgical as well as non surgical approaches to treat drug induced gingival hyperplasia. The primary goal of nonsurgical approaches is to reduce the inflammatory component of the gingival tissues and thus avoid the need for surgery. Patients who have developed drug-induced gingival overgrowth, or even those who are at risk, “will benefit from effective oral hygiene measures, professional tooth cleaning, scaling, and root surface instrumentation” (Bharti 176). In addition, in immunosuppressed patients, giving topical antifungal medications, such as nystatin lozenges, often seems to resolve the problem of gingival enlargement (Bharti 176). One can also apply the pharmaceutical approach and take NSAIDs to control IL-1 mediated inflammation, or take low dose androgen receptor antagonists to decrease collagen production responsible for epithelium thickening (Bharti 176).

Full mouth disinfection using chlorohexidine is first step towards halting DIGH progression

One should also consider discontinuing the offending drug or substituting the medication. Replacing the drug is obviously the better option than stopping the medication completely since that can bring on other medical problems the drug was treating. In all cases, the patient's general physician must be consulted. Common replacements for PHT include carbezamine and valproic acid. Nifedipine can be replaced by isradipine while cyclosporine is better substituted by mycophenolic acid and azathioprine, both of whom are reputed to reduce gingival inflammation. For hypertensive patients, antihypertensive drugs other than calcium channel blockers may be used. If any drug is substituted, it is important to give the new drug a 6-12 month trial because this is how long it takes the previous gingival hyperplasia to resolve completely (Bharti 177).

If however, gingival enlargement continues despite adequate oral care and drug substitution, periodontal surgery might be considered. This may include scalpel gingivectomy, periodontal flap surgery, electrosurgery or laser excision (Bharti 177). The kind of surgery the clinician opts for "will depend upon the extent of area involved, the presence of periodontitis as well as the presence of osseous defects in the gingival lesions" (Bharti 177). For rapid healing time, the use of laser excision is now recommended.

Prognosis

Even non surgical treatment, such as full mouth disinfection, have proven quite beneficial in reducing the symptoms of gingival enlargement in patients. A study conducted at the Rungta College of Dental Sciences in India found that, in DIGH patients who underwent full mouth scaling and root planing followed by disinfection with chlorhexidine gluconate, the plaque index, probing pocket depth and gingival overgrowth improved significantly at the 3 month and 6 month recare appointments (Pundir 312). Not only did the non surgical approach reduce clinical manifestation of the disease, it also decreased the patient's need for surgical intervention, resulting in more efficient time management and less time missed from work.

Although surgery is often more physically invasive and emotionally difficult, requiring a longer time for homeostasis, it works even better than the non-surgical method in preventing recurrence. Those who underwent surgical treatment were able to keep disease free for at least 12 months while those depending on hygiene methods saw no recurrence of the disease for at least 6 months (Bharti 177)

This is in high contrast to no treatment. Without any medical or dental intervention, the disease is likely to continue and the patient will suffer from increased bleeding upon probing, thickened epithelium, larger pocketing depths and eventually bone destruction, tooth mobility and tooth loss. To prevent such clinical manifestations from ruining the speech and occlusal ability of the patient, it is important for the clinician to put the patient on periodontal therapy and halt the disease from progressing (Pundir 314).

Professional Relevance

Every dental hygienist will, at least once in his lifetime, come across a patient who seems to have enlarged/inflamed gingiva that may be caused by a multitude of systemic and oral conditions, including the influx of certain drugs. Dental hygienists play a huge role firsty in

differentiating other gingival lesions from the specific condition of drug induced gingival hyperplasia, and then in healing the patient who is suffering from the latter. Since DIGH looks clinically similar to many types of gingival enlargements, it is important for the DH to take a thorough medical and dental history of the patient, including a search of the medications the patient is taking and their side effects. Because many bone defects and cysts can also give a clinical appearance of gingival overgrowth, it is important for the DH to order radiographs, cytological tests, hematologic examinations as well as microscopic study to differentiate the lesion from other pathology.

Once the cause of the gingival inflammation is rightly attributed to DIGH, it is important for the DH to work closely with the physician to come up with alternative medications to substitute for the drug that might be causing the disease. Furthermore, since secondary inflammation caused by physical irritants such as plaque and calculus, can make the disease worse, it is upto the hygienist to remove all such etiological causes. Therefore, in a patient that presents with gingival hyperplasia, the clinician must carefully debride and disinfect all parts of the mouth. The DH must also propose proper self care to the patient, including adequate toothbrushing and use of oral disinfectants such as chlorhexidine gluconate, to keep secondary causes of gingival hyperplasia at bay and prevent recurrence of the disease (Bharti 177). Lastly, the dental hygienist must establish a shorter recall of 3 months or less for such a patient so his condition can be adequately maintained and he can be referred to a periodontist for further care or surgery if the disease seems to be progressing. The dental hygienist, as the forefront of oral care, plays a huge role in diagnosing, treating and maintaining the disease, and only with his help can the patient fully recover from DIGH.

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