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A Review Article: Modern Minimal Invasive Management and Surgical Treatment of Cyclosporine-Induced Gingival Hyperplasia in Female Adolescent

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Abstract

Drug-induced gingival enlargement was first observed in patients who were taking phenytoin for epilepsy, with approximately 50% having gingival overgrowth. Cyclosporine is an immunosuppressant which has been reported to cause gingival enlargement in 25-80% of patients. Some of the variation in incidence of gingival enlargement can be attributed to differences between study populations and methods of classifying its severity. Gingival enlargement usually develops in a susceptible individual within a few months of starting the medication. Drug-induced gingival enlargement consists of soft tissue growth that begins between the teeth and increases in all directions. As the tissue enlarges it develops a characteristically thickened and lobulated appearance. It may partially or completely cover the tooth surfaces, including the occlusal (chewing) surfaces, as well as extending the other way, into the sulcus. The epithelial surface is usually smooth and fibrotic, but can be nodular in cyclosporine-induced enlargement. If there is underlying periodontal disease then the tissues may be inflamed, red or purplish in color, and highly vascularized, with a tendency to bleed profusely. This review aims to provide the interest to discuss the Modern minimally invasive ways (surgical and non-surgical) for treatment the Cyclosporine-induced gingival hyperplasia specially in female adolescent.

Key words:- gingival enlargement, periodontal disease, Cyclosporine.

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1. Introduction :-

Gingival overgrowth or hyperplasia is an abnormal condition in which there is change in gingival volume and ranges from a slight hyperplasia of the interdental papillae to a growth in which the dental crowns remain completely covered by the altered tissue [1]gingival enlargement has numerous causes, including poor dental hygiene, medications, serious systemic illnesses, genetic conditions, other specific physiologic states, or it may be idiopathic [2].Regarding gingival enlargement associated with medications, some systemically administered drugs are capable of modifying the inflammatory and immune response of periodontal tissues, especially gingival tissue [1] . Cyclosporine is a selective immunosuppressant that has a variety of applications in medical practice[3] ،Cyclosporine is a potent immunosuppressive agent originally used to prevent rejection after organ transplantation but now more frequently used for treatment of autoimmune diseases. It can induce many disorders such as nephrotoxicity, gastrointestinal reactions, and gingival hyperplasia[4]. The onset of puberty can cause change in the hormonal levels which in turn may affect the gingival tissues in females leading to altered tissue response to dental plaque and can lead to gingival enlargement [5]and the management depending upon the severity of condition and general health condition of the patient [6] .

1.1 Gingival hyperplasia:-

one of the commons gingival diseases and can be caused by gingival inflammation, fibrous overgrowth or a combination of the two.[5] It is multifactorial and results from a complex interplay between the host and the environment or can occur in response to various stimuli. Gingival hyperplasia can cause unpleasant response to the inflammation caused by local irritants, such as

plaque and calculus ,systemic disturbances, such as hormonal changes; or medications specifically cyclosporine, nifedipine and phenytoin.[6]Gingival overgrowth is a significants side effect that consequent the use of Cyclosporine . Up to 97% of the transplant recipient kids and up to 90% of the patients submitted to immunosuppressant drugs , who were on Cyclosporine therapy have been reported to suffer from this side effect. Several theories have been proposed to describe the fibroblast's function in Cyclosporine induced gingival overgrowth. Cyclosporine induced gingival overgrowth was investigated in a clinical study of 80 renal transplant patients. 34% of the patients manifest at least mild gingival overgrowth in the anterior, and 9% manifested this finding also in the posterior region. Young and female patients were at a significantly greater risk of developing cyclosporine induced gingival overgrowth than the other patients..[5,6].

1.2 Cyclosporine drug:-

Cyclosporine (CsA) was introduced in 1972 thanks to Borel of the Sandoz pharmaceutical company and registered in 1983. It is a lipophilic cyclic endecapeptide, isolated as an antifungal, from soil samples containing Cylindrocarpon lucidum BOOTH and Tolypocladium inflatum GAMS (fungi imperfecti)[7].

The molecular tertiary structure results in the formation of hydrophilic immunosuppressant binding site and reduces immunosuppressant potential. CsA is variably absorbed in the gut and peak plasma concentration is reached after 3-4 hours. The drug is mostly bound to the following cells: 50% erythrocytes, 5% lymphocytes and 40% lipoproteins , with approximately 5% free in the plasma . CsA is metabolised in the liver microsomes [8] and excreted after 6 hours mainly via the bile, through the faeces . In vitro and in vivo experiments indicated that CsA interferes selectively on T cell, particularly it inhibits T helper cells and it has get or no effect on T suppressor cells .

Cyclosporine A (CsA) has been the primary tool to prevent the rejection of organ transplants. The clinical use of CsA is often complicated by several well documented side effects including gingival overgrowth (GO) (Table 1) [9].

Table 1. Reported side effects of CsA:-

• Nephrotoxicity	• Hypertension
• Hepatotoxicity	• Biliary calculus disease
• Diabetes	• Neurotoxicity
• Epilepsy	• Hirsutism
• Tremors	• Altered bone metabolism
• Lingual fungiform papillae hypertrophy	• Gingival Overgrowth
• Plasmocytoma	• Kaposi's sarcoma
• Squamous cell carcinoma of the lips	• Cephalalgy
• Sinusitis	• Conjunctivitis
• Hairy-leukoplakia	

cyclosporine induced gingival hyperplasia by 1.increased proliferation of human gingival fibroblasts 2.increased gingival keratinocytes proliferation 3.upregulations in expression of salivary inflammatory cytokines IL-1alpha,IL-6,IL-8 4.modulates local expression RAS components angiotensinogen Ang II and its receptors on gingival fibroblasts cells 5.Increased expression of cell surface heparin sulfate proteoglycans 6.inhibition of gingival cell apoptosis [10].

1.3 Hormones associated gingival hyperplasia:-

The Prevalence and severity of gingival hyperplasia has been reported to be significantly higher in children in comparison to the adults undergoing organ transplants. The immature fbroblasts, probably, are more sensitive to the effect of Cyclosporine so the increase gingival hyperplasia in adolescents can be due to an

interaction between circulating androgens, estrogens and gingival fibroblasts. Studies seem to suggest that children, especially adolescents and females may be more susceptible to this side effect than adults, The high-level of sexual hormones found in patients of this age produce an active metabolite (5 alpha-dihydrotestosterone) that acts on a subpopulation of gingival fibroblasts as being to the increase collagen synthesis and/or to decrease the collagenase production [11]. Puberty in femal adolescents associated with changes from maturation into adulthood including increase in sex hormones production:estrogen and progesterone [12] and these hormones effect in different tissues whereas their receptors arefind [5] In gingiva, these steroid hormones can influence the cell division, growth and differentiation of fibroblasts and keratinocytes in addition to the alteration in blood vessels is mostly by estrogen influence and stimulation of the production of inflammatory mediators by progesterone.This at all result in an exaggerated response of the gingival tissues to plaque and can lead to gingivitis or gingival enlargement.[5] gingival tissue and gingival flora influence by hormonal increase at puberty.Microbial change occurs at adolescent and attributed to the changes in the microenvironment in gingival tissues response to the sex hormones and tendency of some bacterial species to proliferate with increasing in hormonal level concentration such as prevotella intermedia ,gram negative anaerobe these species possess the ability to substitute progesterone and estrogen for Vitamin Kas an essential growth factor for this microorganism.[5]. In addition to neglect oral hygiene in this age where the food debris,material alba, plaque and calculus are deposit and bacterial proliferation occurs lead to noduler hyper plastic reaction of gingival tissues [12].So it’s important in management at this age group a conventional periodontal therapy comprising of scaling and root planing is sufficient to treat the conditionand in more fibrotic tissues can managed by gingivectomy by scalpel or periodontal knives, Electro surgery and LASER. [5].

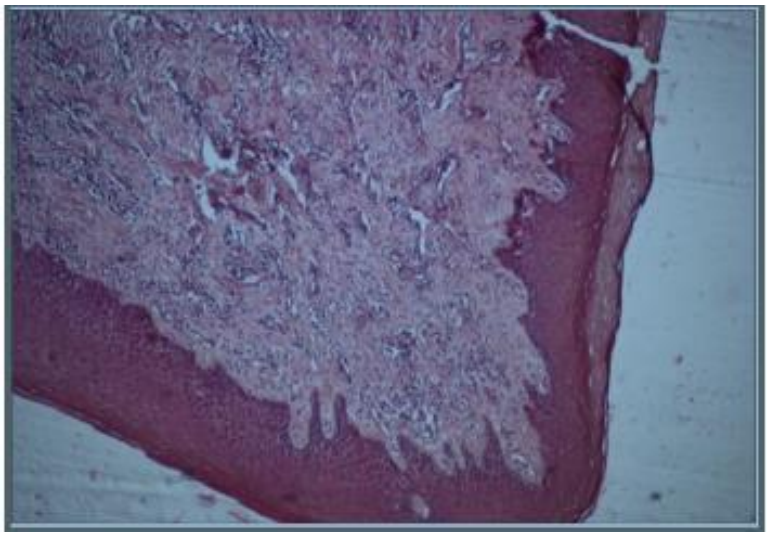

Figure 1: H & E staining showing parakeratinized stratified squamous epithelium with elongated rete ridges and connective tissue with collagen bundles arranged in whorled pattern.

1.4 Related causes to gingival hyperplasia:-

Orthodontic therapy can change oral hygiene accessibility and complicate periodontal health . The mechanical irritation from the orthodontic appliance can cause local inflammatory responses in the gingival tissues . orthodontic therapy in addition to the gingival sulcus and subsequent plaque accumulation which results, further complicate the efficiency of salutary orthodontic care, the area between the brackets and gingival margin tends to have greater plaque accumulation due to difficulty in cleaning the teeth associated with the placement of an orthodontic appliance and increased in sex hormones at puberty increases the complex of the problem and gingival inflammatory response to the dental plaque .The gingivitis can occur at 1-2 months after orthodontic placement even at good oral hygiene.[13] Localized juvenile spongiotic gingival hyperplasia is a localized erythematous lesion of the anterior attached gingivae. Presenting in a peri-pubertal age, this

condition is often misdiagnosed as puberty gingivitis[14] seen in young patients (average age 11.8 years) predominantly female and generally found in the maxillary anterior region mainly seen in conjunction with orthodontic brackets.(figure 2) [15]Histologically the spongiotic lesion is observed which is covered by nonkeratinized epithelium with elongated ridges, pronounced edema of 5 the spiny layer, exocytosis of neutrophils, dilated capillaries, as well as, mixed inflammatory cell infiltrate are visible in the lamina propria [16]

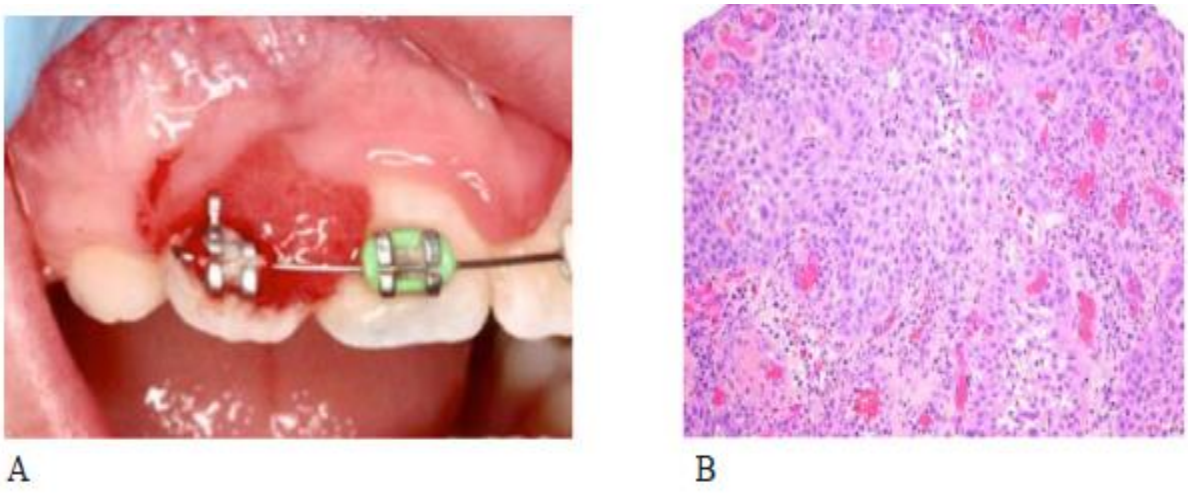

Figure 2: A) clinical presentation for orthodontic induce gingival hyperplasia. B) histological view for gingival hyperplasia induced by orthodontic appliance.

The treatment of choice has not been determine some studies show that surgical excision with scaling and root planning of adjacent teeth and carbon dioxide laser could be the treatment of choice.[15,16] and conservative therapy, a mild surface cauterization followed by topical application of a 0.05% clobetasol ointment four times per day for a period of 4 weeks, thereby avoiding potential gingival margin defects that may result from a surgical ablation of the lesion[17]

2. Pathogenesis:-

The precise mechanism of cyclosporine-induced gingival overgrowth is uncertain. Various investigations for pathogenesis of gingival overgrowth support the hypothesis that it is multifactorial[18]. A possible model is shown in Figure 3 Cell culture studies have shown that both cyclosporine and cyclosporine metabolites have direct effects on gingival fibroblast proliferation, protein synthesis and collagen production [19]Furthermore, there exists a genetically determined subpopulation of cyclosporine sensitive gingival fibroblasts. Indeed, the terms "responders" and "nonresponders" have appeared in the literature to identify those who show or do not show drug-induced gingival changes. Both findings are important in the pathogenesis of cyclosporine-induced gingival overgrowth.[20]

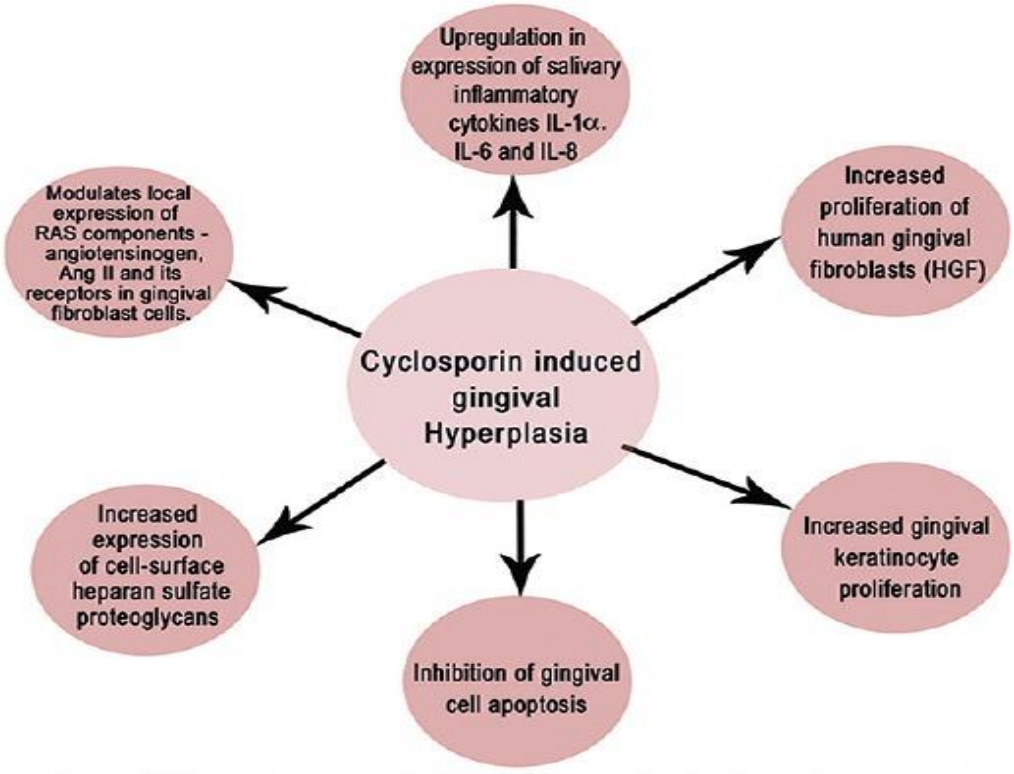

Figure 3 Pathogenesis of cyclosporine A-induced gingival overgrowth: Model depicting the various mechanisms by which cyclosporine A causes gingival enlargement.

3. Treatment of gingival hyperplasia:-

3.1 Plaque control and medical management:-

Mild gingival hyperplasia may only require local management as improvement in oral hygiene, with cleaning of the teeth, can lead to resolution of inflammation and reduction in gingival hyperplasia.. debridement with scaling and root planing as needed has been shown to offer some relief in gingival overgrowth patients[3] Mild gingival enlargement will often diminish with removal of plaque and calculus deposits [21]Treatment planning becomes more complex where there is periodontitis associated with gingival enlargement, which poses a cosmetic or functional problem. Oral hygiene has benefit in moderate gingival hyperplasia also by reducing it and avoid surgical removal, but there's minimal benefit on sever gingival hyperplasia[21]. Chlorhexidine 0.1% should be rinsed 2-3times daily for the first few postoperative days, with careful mechanical cleaning introduced gradually as it becomes more comfortable [21]and has been reported to inverse recurrent Cyclosporine overgrowth following gingivectomy[6] cyclosporine which is the drug of choice in kidney transplant patients ,So one of the important things in management of all drug induced gingival overgrowth is drug substitiution, reduction in the dose of cyclosporine has been shown to be beneficial, [6] Some patients can use more conventional immunosuppressant such as steroid and azathioprine but survival rate are not as good new immunosuppressant such as tacrolimus (FK 506) (Prograft), rapamycin and mycophenolate mofetil (MMF) may offer some hope, as to date these have not been reported
in association with gingival overgrowth.[6] and recent update found the Azithromycin reduce the effects of cyclosporine induce gingival hyperplasia[22]. Changing from cyclosporin to tacrolimus can be considered if significant gingival enlargement recurs after excision.

Tacrolimus has a different toxicity profile and is not associated with gingival enlargement [21] Tacrolimus is a xenobiotic immunosuppressant which has demonstrated high clinical efficacy to avoid graft rejection in solid organ transplants, through an action mechanism based on the inhibition of the calcineurin pathway, in study in 2003 on four patient who are organ transplant 7 recipients and had gingival hyperplasia induced by cyclosporine administration where they found the four patients showed a rapid decrease in their gingiual symptoms and in the size of the gingiva .. This change was clinically evident 8 weeks after conversion to tacrolimus alternative with oral hygiene program.One year later, al1 the patients experienced GE regression, although someanatomic irregularities persisted in the interdental papillae of one of the patients. No adverse effects from tacrolimus were observed during the study except in one case who presented headaches.[23] It was reported that the chance of having gingival enlargement were five times higher among renal transplant patients on cyclosporin than among those on tacrolimus [24]. There's usually a recommendation for prophylactic antibiotics, Nonsteroidal anti-inflammatory drugs and antibiotics such as erythromycin and clarithromycin are not recommended. They may interfere with cyclosporin and could raise the serum levels, rendering the patient more immunosuppressed than desired [24]

3.2 Diode laser:-

Diode lasers proposed as one effective surgical tool in the management of this highly vascular tissue. To compare conventional surgical excision with laser therapy Figure 4, for treatment of inflammatory gingival hyperplasia [25]The biological mechanisms of laser action depend on laser parameters and tissue properties. Laser parameters include wavelength, exposure time, power setting, pulse duration, spot size, and other parameters such as the direction of the laser beam and the speed of movement . Different types of lasers are been used in

dentistry includes CO2, Nd: YAG, diode lasers and Erbium family lasers.[26]The adjunct use of diode laser gingivectomy combined with oral hygiene can produce quicker and greater improvement in gingival health, suggesting its beneficial use for orthodontic patients with gingival hyperplasia.

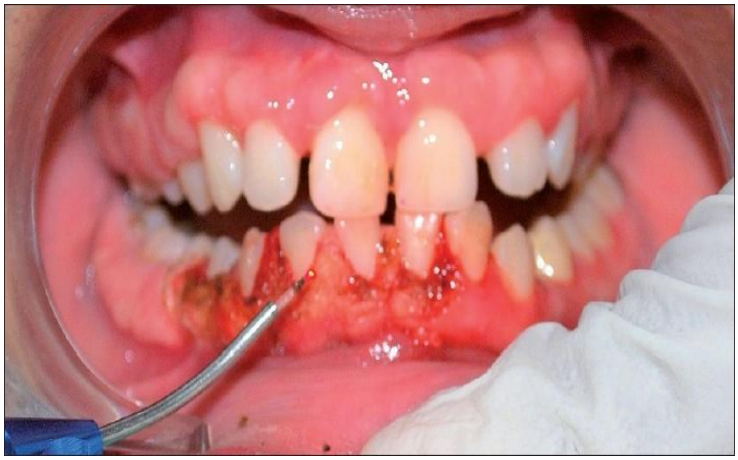

Figure 4. Diode lasers showed an effective surgical tool in the treatment of gingival hyperplasia.

Thirty patients who are undergoing fixed orthodontic therapy with gingival hyperplasia divided into two groups ;one group tested by receiving diode laser gingivectomy alternative with non surgical periodontal treatment and another group controlled by receiving non-surgical treatment only.These patients monitored at baseline, 1month,3months and 6 months for five parameters (plaques index ,gingival index,bleeding on probing ,probing pocket depth and gingival overgrowth index) in results both groups showed improvement in periodontal health but there's significant earlier improvement in periodontal health in tested group with diode laser more than controlled group with non surgical therapy only [27]. The CO2 laser has been advocated because of the decreased surgical time, rapid postoperative hemostasis and the fact that often the underlying medical conditions are relative contraindications for conventional surgery[6].

3.3 Surgical management:-

The need for surgical treatment to be carefully assessed. Surgery is normally performed for cosmetic/aesthetic requests before any functional need is showed [11].The classical surgical approach has been the external bevel gingivectomy .the total or partial internal gingivectomy approach has been suggested as an alternative. This is a more technically demanding approach, which has the benefit of limiting a large denuded connective tissue wound that results from the external gingivectomy, thereby minimizing postoperative inflammation, pain and bleeding [28].In cases where drug therapy is likely to continue for many years, psychsocial consideration need to be considered in an effort to reduce the frequency and the extend of any surgical intervention. While classical external bevel gingivectomy is still a viable treatment option, the large denuded connective tissue wound that result can be painful and requires careful postoperative care to prevent infection. There is a tendency towards the use of either a total or partial internal bevel gingivectomy approach. This technically more demanding approach have the benefit of allowing 'primary closure' thus reducing the chance of post operative complications, however it requires more time and skill to a accomplish.

Surgical treatment of PHT-, Cs and CCB-induced gingival overgrowth has centered on gingivectomy by conventional methods [8]and there are many types of procedures: Electrosurgery :by applies electric currents on gum tissue to cut or remove overgrown,Periodontal flap surgery :in this procedure separates the gums from the teeth .The gums are folded back temporarily to allow the periodontist access to remove inflamed tissue and clean any plaque. Gingivectomy: removes a portion of the gums from around the teeth and then repair the remaining gums with stitch [29].

4. Results:-

Twenty-two eligible articles were included in this study. Management approaches included discontinuation or change of the offending medication if medically feasible in addition to surgical and nonsurgical interventions. Nonsurgical approach included scaling and root planing, oral hygiene instructions, and antimicrobial mouthrinses. Persistent or relapsed cases had complete resolution with excision of hyperplastic gingiva. Laser-assisted surgeries combined with intensive plaque control measures demonstrated less risk of recurrence.

5. CONCLUSION:-

Gingival hyperplasia serious condition can induce by cyclosporine administration with multiple factors can aggressive that affect and puberty period in female adolescent one of this factors aggravated the conditions by increased hormonal level and their effect on gingival tissues , the neglect of oral hygiene at this period can help in bacterial proliferation and aggravate the gingival enlargement.The condition can management as non-surgical treatment by oral hygiene with cyclosporine reduction or withdrawal and surgical treatment by gingivectomy and recently using of laser become mor significant due to its properties by decrease surgical time, reduce bleeding and in contraindications surgery conditions .

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