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Drug induced hyperplasias- A case report

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Abstract
Drug-induced hyperplasia or gingival overgrowth (DIGO) is a well-recognized adverse effect of certain systemic medications. Calcium channel blockers, anticonvulsants, and immuno suppressants are frequently implicated drugs in the etiology of DIGO. The three important factors in the expression of gingival changes after systemic medication use are drug variables, plaque-induced inflammation and genetic factors. The basis for diagnosis of DIGO is careful clinical examination and thorough history taking. For differential diagnosis histopathological examination is an important aid. The purpose of the present case report is to assimilate and compile the information for clinical applications such as diagnosis and therapeutic management of DIGO.

Keywords: anticonvulsants, drug-induced gingival overgrowth, immuno suppressants

Introduction

Certain gingival diseases that are modified substantially by the use of systemic medications are now well recognized. In the 1999 international workshop for a classification of periodontal diseases and conditions, “drug-influenced gingival enlargements” have been identified and added as a subcategory under the section “dental plaque-induced gingival diseases [1]. The definition for drug-influenced gingival enlargement is “ an increase or overgrowth in size of the gingiva resulting in whole or in part from systemic drug use [2].

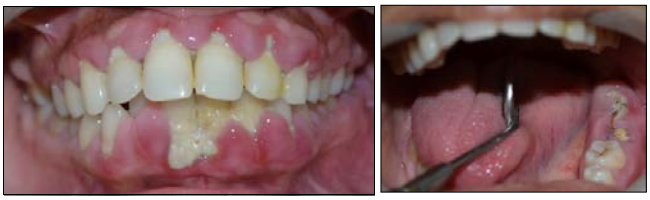
Anticonvulsants such as phenytoin and immuno suppressants such as cyclosporine and calcium channel blockers (CCBs) are frequently implicated as drugs that cause gingival overgrowth [3]. In addition, drugs such as sodium valproate [4] and erythromycin [5] induced gingival enlargements have also been reported in the past. Although the chemical nature of the three drug groups is different, they have a similar mechanism of action at the cellular level, where they inhibit intracellular calcium ion influx. Thus, all these drugs, despite being dissimilar, have a common side effect upon secondary target tissue such as gingival connective tissue [6].

Drug-induced gingival hyperplasia or overgrowth (DIGO) is usually esthetically disfiguring and interferes with speech and mastication. The clinical characteristics common to all DIGOs include a variation in the inter- or intra-patient pattern of enlargement; a tendency to occur more often in the anterior gingiva; a higher prevalence in younger age groups; onset within 3 months of drug use; and no association with attachment loss or tooth mortality. Moreover among the gingival enlargements induced by one drug to another, the clinical lesions and their histological characteristics are indistinguishable [7]. The known risk factors for DIGO are age and other demographic variables, drug variables, concomitant medications, periodontal variables, and genetic factors [3].

In the present case report, we have discussed about induce gingival overgrowth, their diagnosis and therapeutic managements.

Case Report-1

Gingival Hyperplasia Associated With Phenytoin



(a) (b)

Fig 1: a, b - Phenytoin induced gingival hyperplasia

A male patient reported with gingival swelling with pain and bleeding while brushing. Also associated with foul smell and difficulty in eating. The gingival swelling was present since the past 2.5 years. A careful medical history of the patient was recorded, which revealed previous episodes of epileptic convulsions since the past 3 years; however history of any other systemic disease was negative. On general examination, the patient was healthy with normal gait and gesture. Clinically the swelling appeared non-inflammatory and fibrous.

The patient was under medication for epileptic convulsions since the past 3 years. The patient was prescribed Phenytoin, phenobarbital and cefoxitine by his physician and was taking these medicines regularly since the past 3 years. Orthopantomogram radiograph of the patient revealed interdental bone loss in the maxillary and mandibular anterior teeth. Surgical excision of the enlarged gingival

tissue was planned. Before surgical excision, thorough oral prophylaxis of the patient was performed. Surgical excision was performed under local anaesthesia. The gingivectomy and gingivoplasty procedures were performed with the help of scalpel no. 12 and 15, periodontal knives (Kirkland and Orban's knives) and curettes. Following surgical excision, a surgical dressing and periodontal pack was placed. The excised tissue was sent for histopathological and immunohistochemical examination.

Case Report 2

Immuno suppresant Induced Gingival Hyperplasia

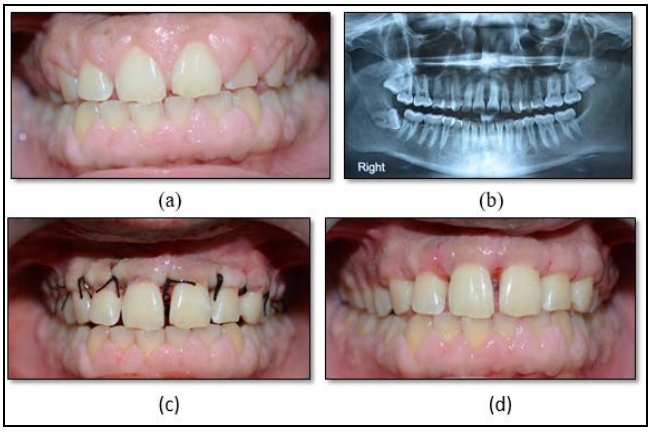


Fig 2: a, b c, d-Immunosuppressant induced gingival hyperplasia

A 28 year old male patient complained of gingival swelling with pain and bleed on brushing. On taking past medical history he had renal transplantation and he is on long term immuno sppressive drug (cyclosporine) for prevention of rejection. Intraoral examination revealed severe generalized gingival hyperplasia. The patient was asserted about the cause of his problem which was related to long term cyclosporine immunosuppressive treatment and treated by gingivectomy

Discussion

Gingival overgrowth is due to intake of certain systemic drugs which is frequently encountered or having unrelated adverse effect. An understanding of the underlying factors and mechanisms involved might be needful in prevention and therapeutic management of DIGO. Seymour *et al*. in 1996 [8] suggested that DIGO is multifactorial and that three factors are significant in its expression. They are drug variables, plaque-induced inflammatory changes in the gingival tissues, and genetic factors. From the reported cases in the last two decades assessed in this review, it has been clear that CCBs, cyclosporine, and phenytoin are the attributing drugs for a majority of DIGO cases. An immunosuppressant reportedly used in kidney/heart/liver transplant patients to prevent organ rejection is cyclosporine [9-21]. It has also been used for treating aplastic anemia [10, 22-23] psoriasis [24] and disease [25] Cyclosporine is known to alter the metabolism of gingival fibroblasts and also upregulates specific growth factors such as platelet-derived growth factor B, thereby causing adverse gingival changes such as overgrowth [6]. Cessation of the drug or its substitution by another drug is a definitive step in the management of cyclosporine-associated gingival overgrowth. Mathur *et al*. in 2003 [13] reported regression of gingival overgrowth in a renal transplant patient after cessation of cyclosporine. Similarly, V'lckova-Laskoska in 2005 [24] reported virtually complete reduction of gingival enlargement after cessation of cyclosporine in a patient under treatment for psoriasis. However, abrupt cessation of an immunosuppressant might lead to severe complications such as failure of organ transplantations. Hence, substitution of cyclosporine by a better alternative has been suggested. Kennedy and Lindenin 2000 [19] and Hernández *et al*. in 2003 [14] reported rapid reduction in gingival overgrowth after cyclosporine withdrawal and its conversion to tacrolimus in organ transplant patients. Similarly, Gonçalves *et al*. in 2008 [10] reported that DIGO in a 9-year-old renal transplant patient under cyclosporine therapy recurred even after surgical correction and thorough practice of plaque control measures, which however regressed on change of medication from cyclosporine to tacrolimus without any need for further surgical intervention. Furthermore, Macartney *et al*. in 2009 [26] reported that gingival enlargement in a child with severe aplastic anemia under cyclosporine therapy did not respond to intensive dental intervention. Significant improvement in gingival hyperplasia could only be achieved after the immunosuppressive therapy was changed to tacrolimus.

CCBs are therapeutic agents that are used in the management of heart diseases, particularly hypertension. CCBs affect calcium metabolism by reducing Ca^{2+} cell influx, which in turn reduces uptake of folic acid and leads to reduced production of active collagenase.[27] Among CCBs, nifedipine is the most frequently implicated drug, inducing gingival overgrowth.[27] However more cases of gingival overgrowth have been reported after amlodipine use than nifedipine in the last two decades (25 cases of amlodipine as against 13 cases of nifedipine). Low doses and short-term administration of CCBs might also induce gingival hyperplasia as suggested by Lafzi *et al*. in 2006 [28] and Joshi and Bansal in 2013 [29]. Furthermore, a case report by Sunil *et al*. in 2012 [30] suggests that severity of the enlargement is dose dependent.

Changes of drug and meticulous oral hygiene are important aspects in the management of CCB-associated gingival overgrowth. Aldemir *et al*. in 2012 [31] reported a case of gingival overgrowth in a hypertensive patient under amlodipine therapy, in which, change of medication resulted in regression of the overgrowth within 3 months without any need for surgical intervention. Joshi and Bansal in 2013 [29] reported that gingival overgrowth in a hypertensive patient under amlodipine therapy showed drastic improvement within 1.5 months after change of drug. Similarly, Ramsdale *et al*. in 1995 [32] reported gingival hyperplasia in a patient with heart disease under long-term nifedipine therapy, which disappeared completely within 6 months after cessation of nifedipine use. On the contrary, D'Errico and Albanesein 2013 [33] reported a case of gingival overgrowth in a hypertensive patient under amlodipine therapy, where only surgical excision of the overgrowth permitted resolution of the case while changing drug and execution of a professional oral hygiene treatment did not allow resolution of the hyperplasia. Leaving the two extremities apart, in case of moderate regression of the lesion, majority of them were managed by change of drug and meticulous plaque control. This was followed by surgical correction of gingival tissues for optimal gingival health and maintenance.

Phenytoin is the most commonly prescribed anticonvulsant agent in the management of epilepsy. Phenytoin-induced gingival overgrowth is the earliest known DIGO; first case of which was reported in 1939 by Kimball [34]. Phenytoin affects metabolism of certain fibroblast subpopulations, intracellular calcium metabolism, reduces folic acid uptake and metabolism, leading to production of inactive collagenase; thus, leading to gingival overgrowth [6]. Rarely, phenytoin is also known to induce mucosal hyperplasia in denture wearers, besides gingival hyperplasia [35]. Dhingra and Prakash in 2012 [36] reported a rare case of enlargement of mucosa in partially edentulous alveolar ridges despite not using any denture, after combination therapy of phenytoin and phenobarbital for epilepsy. Chee and Jansen in 1994 [37] reported a case of peri-implant tissue hyperplasia after phenytoin therapy for epilepsy.

The management of phenytoin-induced gingival overgrowth is similar to that of other DIGOs. The sequential steps in the treatment of phenytoin-associated gingival hyperplasia are withdrawal and change of drug, meticulous oral hygiene maintenance, conservative nonsurgical approach followed by surgical intervention if necessary.

Polypharmacy can have an effect on DIGO. Majority of conditions need a combination therapy, particularly organ transplant patients receiving immuno suppressants are frequently administered CCBs to prevent serious life-threatening complications. However, such concomitant medications have a significant synergistic effect on gingival changes and increase the chances of recurrence [38].

Conclusion

Multifactorial adverse effect of taking certain systemic medications is DIGO. Although exact pathogenic mechanisms are not yet completely understood, the drug variables, dental-plaque induced inflammatory changes, and genetic variables are frequently listed as important risk factors for DIGO. Careful selection of drug and its dose for particular medical conditions by medical practitioners might be helpful in preventing drug-related adverse effects. In cases, where using drugs that induce gingival overgrowth is unavoidable, dental referral, thorough plaque control, reinforcement of oral hygiene maintenance instructions to the patient might be helpful in preventing as well as controlling the severity of the lesion. An in-depth knowledge of pharmacokinetics of the drugs, their adverse effects, pathogenic mechanisms involved in DIGO and their varied clinical presentations helps the dental practitioner in therapeutic management of DIGO. In addition, coordination between medical and dental practitioners is essential for successful management of DIGO.

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