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CASE REPORT OPEN ACCESS

PHENYTOIN INDUCED SEVERE GINGIVAL ENLARGEMENT IN A SPECIAL CHILD-A CASE REPORT

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ABSTRACT

Drug induced gingival enlargement is the most common cause of gingival enlargement in children. The drugs which are usually implicated are Anti-epileptic drugs like Phenytoin, Sodium Valproate, Calcium Channel blockers like Nifedipine and Verapamil. Phenytoin has been used for treatment of epilepsy in children since many decades inspite of the adverse effect of Gingival enlargement. Treatment of this enlargement mainly involves removal of local irritants and most importantly replacement of the offending drug. This case report throws light on a unique case of severe gingival enlargement in a special child.

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INTRODUCTION

The terms overgrowth or enlargement or hyperplasia or hypertrophy are clinical descriptive terms. The term gingival enlargement is a histological term used to describe the increase in the size of an organ due to increased number of cells. Hyperplasia should be distinguished from hypertrophy, which is an increase in the size of an organ as a result of increase in size of its individual component cells with a view of meeting increased functional requirements for useful work (Doufexi, 2005 and Glickman, 1950). Epilepsy occurs in 0.5 to 1% of the population and begins in childhood in 60% of the cases. Incidence is highest in the first year of life. But it can also be seen in other age groups (Suneja, 2016). Among the pediatric population, it usually starts as febrile convulsions which is usually seen in early childhood. It is also commonly seen in children having neurologic deficits as in case of Intellectual impairment and Cerebral palsy. A number of antiepileptic drugs have been used to treat seizures. Gingival overgrowth has been recognized since many decades as a deleterious effect of different anti-epileptic medications.

Classification of Gingival enlargement. Many classifications have been proposed

Glickman's classification according to underlying Histopathological changes and etiology:

I. Inflammatory
   A. Chronic inflammatory gingival enlargement: Generalized or localized and Discrete (tumor like)
   B. Acute inflammatory gingival enlargement (gingival abscess): Marginal and Diffuse
II. Non-inflammatory hyperplastic gingival enlargement (gingival hyperplasia)
III. Combined gingival enlargement
IV. Conditioned gingival enlargement
   A. Hormonal
      1. Gingival enlargement of pregnancy
      2. Gingival enlargement of puberty
   B. Leukemic gingival enlargement
   C. Gingival enlargement associated with vitamin c deficiency

V. Neoplasms
Vi. Developmental gingival enlargement

According to location: -Enlargements could be marginal, papillary or diffuse.

Based on distribution they can be localized or generalized (Glickman, 1950). Localized enlargements could be further divided into three sub-types, i.e., isolated, discrete and regional. It can also be scored as Grade 0: No signs of gingival enlargement; Grade I: Enlargement confined to interdental papilla; Grade II: Enlargement involves papilla and marginal gingival; and Grade III: Enlargement covers three quarters or more of the crown (Doufexi, 2005).

Drug induced gingival enlargement: The association of phenytoin with gingival enlargement was first described by Kimball in 1939 (Kimball, 1992). Drug-induced gingival overgrowth is a known adverse effect with phenytoin being the most common, Sodium valproate antiepileptics cyclosporine A, an immunosuppressant; and calcium channel blockers, such as nifedipine, diltiazem, and verapamil, which are widely prescribed for the treatment of various cardiovascular diseases. This is characterized by an accumulation of extracellular matrix within the gingival connective tissue, particularly the collagenous component, with various degrees of chronic inflammation (Bharti, 2013).

Case report

A female patient aged 17 years, reported to the Department of Special Health care needs at SDM Dental college, a constituent unit of SDM University with the chief complaint of pain in lower right back tooth region and tongue trap leading to difficulty in eating. Parents gave past medical history of surgical correction of Cleft lip and Palate at one year of age. History of Cerebral palsy and Epilepsy was also revealed. First attack of Epileptic Seizures was at 3 years of age and on an average of about 10 attacks per day. The last attack was in the month of January 2019 and she was hospitalized for the same.

Pre-surgical photographs

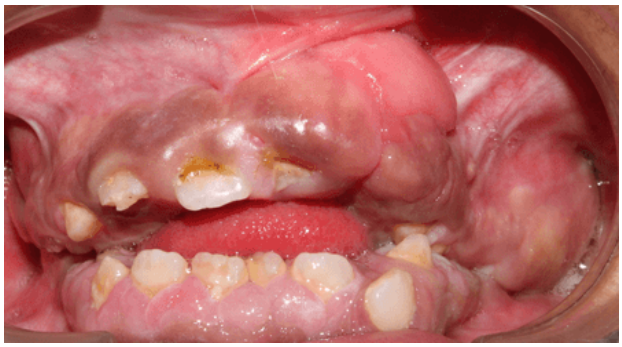

Figure a. Frontal view

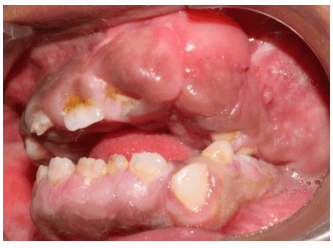

Figure b.1. Left Lateral view

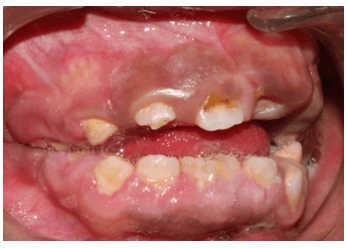

Figure b.2. Right lateral view

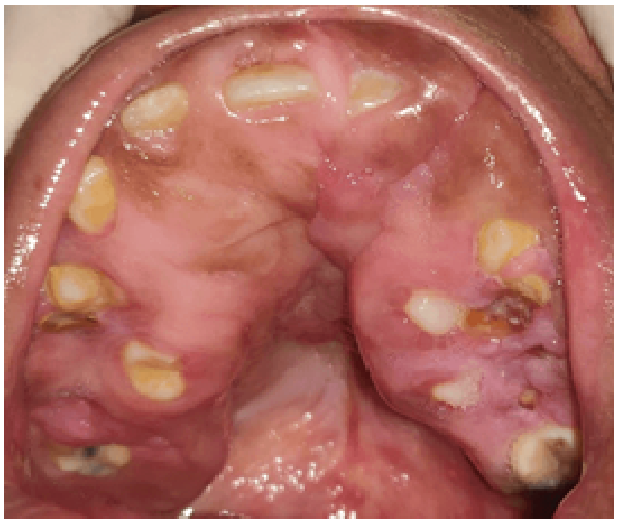

Figure c. Intra oral view of maxillary arch

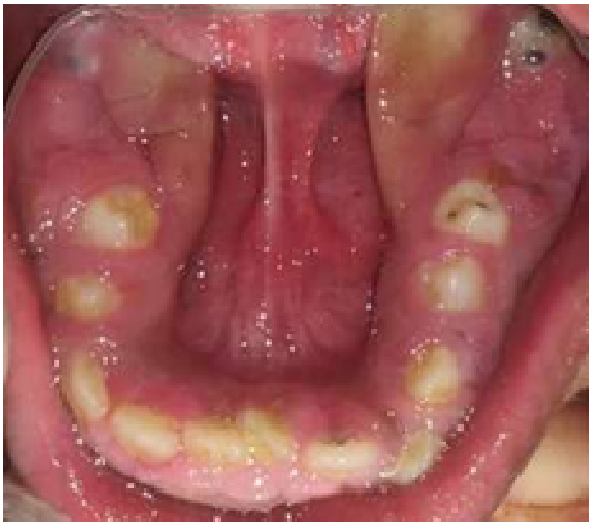

Figure d. Intra oral view of mandibular arch (arrows indicating extension of the enlargement into the tongue space)

Drug history: Tab Sodium Valproate for the first three years followed by Epilex for 11 years. Three months back Epilex was replaced by Eptoin and Gardinal-50 mg twice a day and Frisium syrup taken only in case of high fever.

Behavioral concerns: During examination patient was aggressive and restless, uncooperative behavior and inability to follow instructions.

On intra oral examination: Inspection-It was red in color because of the inflammation and Grade III gingival enlargement with both upper and lower arches covering the teeth with the incisal thirds of 11, 12, 13, 14, 15, 54, 21, 23, 24, 25, 65 , 26 in the maxillary arch and in the mandibular arch incisal thirds of 41,42,43,44,45,31,32,33,34,35 were visible. The gingiva was red, boggy, edematous and easily bled on probing. The enlargement had led to ectopic eruption of 15 and 25 palatally. The enlargement in the mandibular posterior region was so severe that it had extended on the tongue and hampered tongue movements.

Palpation: The gingiva was fibrotic, leathery and firm in consistency, stippling was absent. Provisional diagnosis of

Phenytoin induced enlargement was made based on history and clinical findings.

Investigations: OPG was made and IOPA radiographs could not be taken as she was uncooperative.OPG showed root stumps with 16, 36, 46, 64, 65, 74 and 75 which were not clinically visible.

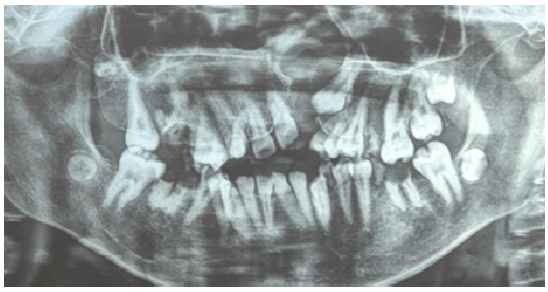

Figure e. Orthopantomograph

Treatment plan was charted which included scaling followed by gingivectomy and extractions. The procedure was explained, and consent taken. Considering the patients well-being and difficulty to perform procedure on dental chair, case was electively chosen under General Anesthesia after pre-anesthetic evaluation. Gingivectomy procedure was performed by placing Internal bevel incisions using 15 size blades with Bard-parker handle number 3 and gingival contouring was done. Multiple blades were changed as the gingiva was very fibrous and thick. Extractions of root stumps with 16,36,46,64,65,75,54 were done. Extraction of 15 and 25 was done as they had ectopically erupted and could create difficulty in maintaining oral hygiene. Excised tissue was sent for Histopathological evaluation. This surgical procedure was unique due to the extent of enlargement and the thickness of fibrous gingiva. Coe-pak was placed and the patient was recalled after 3 days.3-0 Vicryl sutures were placed in 46 and 36 regions. The patient was recalled after a week for overall follow up check. Good tissue healing was seen after one week of follow up. There was considerable reduction in the gingival size.

Post-Surgical follow-up photographs

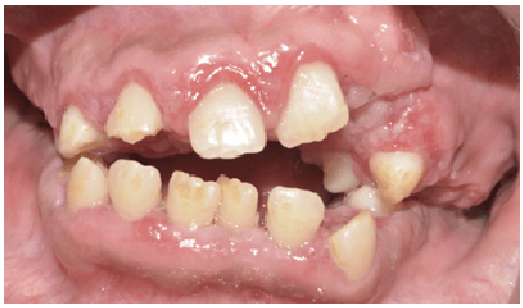

Figure f. Frontal view

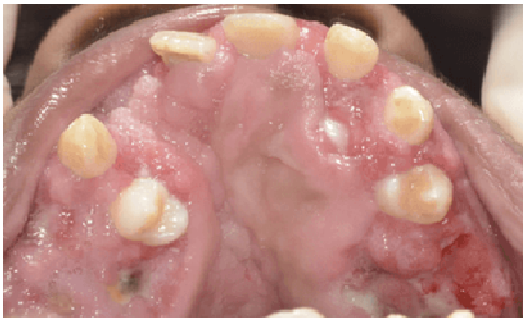

Figure g. Intra oral view of maxillary arch

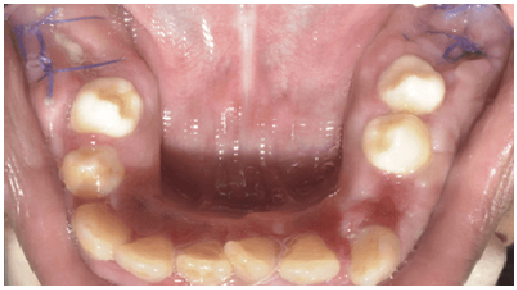

Figure h. Intra oral view of mandibular arch (we can see the sutures in 36, 46 region)

DISCUSSION

Phenytoin has been used to control seizure disorders in patients with epilepsy since its clinical introduction by Merritt & Putnam in 1938. Within a year of its initial clinical use, reports linking phenytoin to gingival overgrowth appeared in the literature**.** Due to the effectiveness of this medication in controlling convulsive seizure disorders and its low cost and availability, phenytoin has entertained sustained and extensive use for this purpose over the last 80 years. Along with Phenytoin various other anti-epileptic drugs like Sodium Valproate, Carbamazepine, Ethosuximide, Primidone and Calcium Channel blockers like Ethotoin, Amlodipine, Bepridil, Diltiazem, Felodipine, Nifedipine also cause gingival enlargement (Hallmon, 1999). Dill *et al*. have proposed that phenytoin increases the production of platelet-derived growth factor, a dynamic cytokine involved in the process of connective tissue growth and repair, and that excessive platelet-derived overgrowth. Using in situ hybridization, the authors demonstrated that phenytoin facilitated the expression of the gene for platelet-derived growth factor-B expression (c-sis), thereby explaining the occurrence of gingival overgrowth (Dill, 1993). A strong correlation has also been observed between production of inactive collagenase and phenytoin exposure of responder fibroblasts. These cells produced and secreted more collagenase (active and inactive) than human gingival fibroblasts from nonresponders. Phenytoin may also interfere with and reduce polyhydroxylated production, an enzyme responsible for post-translational hydroxylation of prolyl residues during collagen synthesis. In addition, phenytoin can also decrease the activity of collagenase (Hallmon, 2000).

In summary, while the pathogenesis of phenytoin induced gingival overgrowth has not been determined, evidence suggests a direct effect on specific subpopulations of fibroblasts, genetic predisposition, intracellular calcium metabolism exchange, molecular mechanisms (cytokines such as epidermal growth factor, platelet-derived growth factor-P), inactivation of collagenase and inflammation induced by bacterial plaque. These dynamic variables may act on the gingival milieu individually or collectively to alter the homeostatic steady state present in health (Dill, 1993; Dahllof, 1986; Modeer, 1990; Moy, 1985; Hassell, 1981and Vernillo, 1987). Current literature suggests that genetic factors might be implicated in the pathogenesis of gingival enlargement in children and adolescents. Not all patients who are on phenytoin, cyclosporin, or nifedipine develop gingival overgrowth. Patients are characterized as “responders” or “non-responders” based on the presence or absence of gingival overgrowth (Seymour, 2000). It is characterized by initial enlargement of the interdental papillae and is less frequently

accompanied by increased thickening of the marginal tissue**.** Affected tissues typically present a granular or pebbly surface, with the enlarged papillae extending facially and/or lingually, obscuring the adjacent tissue and tooth surfaces. Affected papillae may become enlarged to the point that they contact, resulting in the clinical presence of pseudo clefts**.** Although florid tissue overgrowth usually diminishes as it approaches the mucogingival junction, coronal progression may partially or totally obscure the crowns of the teeth (Kumar, 2014).

The facial gingiva of the anterior sextants is more commonly affected and often results in aesthetic disfigurement. There is no evidence suggesting that sex or race affects the occurrence of phenytoin associated gingival overgrowth. Enlargement of the gingival tissues may result in malpositioning of teeth and interference with normal masticatory function, speech and oral hygiene. There are also reports of phenytoin-induced gingival overgrowth prior to the eruption of the primary teeth, which resulted in delayed eruption (Steinberg, 1985; Rabcock, 1965 and Davis, 1963). In the present case, the gingival enlargement was most severe in the maxillary and mandibular posterior regions. In the mandibular posterior region, the enlargement had flattened bilaterally due to occlusal forces and the tongue movements were hampered due to it. The marginal, interdental and attached gingiva was enlarged leading to severe malpositioning and ectopic eruption of 15 and 25 palatally. Dahllof *et al*. studied the effect of phenytoin withdrawal in 10 children with previously developed phenytoin gingival overgrowth. Significant regression of the condition was observed at 1 month, and the buccal-lingual gingival dimensions were comparable to, a control group of children taking other antiepileptic drugs when evaluated at 6 months post-phenytoin withdrawal. These observations were made without patients receiving professional prophylaxis, and the regression interval coincided with the 1-month period generally required for gingival overgrowth to appear after initiating phenytoin therapy (Dahllof, 1991 and Dahllof, 1986).

Treatment and prevention of Phenytoin induced gingival enlargement: This must be done as a two-step procedure. First the local irritants have to be removed and scaling to be done. The next step would be gingivectomy and gingivoplasty. The most important step here is the drug which has to be replaced to prevent recurrence. Oral hygiene maintenance is extremely important to the preventive and therapeutic management of drug-induced gingival overgrowth and should be instituted prior to starting such therapy whenever possible. Although scaling and root planning effectively reduces accompanying inflammation, surgical treatment is often required to manage the consequences of clinically significant gingival overgrowth (Jones, 1986). The excessive tissue can be removed using conventional surgical techniques (gingivectomy/ flap), laser gingivectomy or a combination approach. A vacuum-formed surgical stent lined with periodontal dressing or tissue conditioner may facilitate control of postoperative hemorrhage and protection of the surgical wound (Pihlstrom, 1990). Positive pressure appliances have been recommended as a means of preventing or reducing the recurrence of gingival overgrowth. A long-term maintenance and recall follow-up program should be instituted consisting of medical history update and re- view, evaluation, prophylaxis and reassessment and reinforcement of oral hygiene. Oral antimicrobial agents should be considered as a treatment adjunct and may prove beneficial, especially following surgical reduction of gingival overgrowth (Rabcock, 1965 and Davis, 1963). In the present case, the Maintenance phase included anti microbial mouth rinse in which the parents were explained and demonstrated the use of gauze to be wrapped around the finger and to be wiped on the gingiva twice a day as the patient showed incapacity to rinse. On the 15th day follow up visit, the parents were satisfied as she could have food with discomfort and tongue movements had improved. Further the parents were instructed for the regular follow up as the patient would continue anti-epileptic drugs and there could be chance of recurrence of gingival enlargement.

Histological appearance

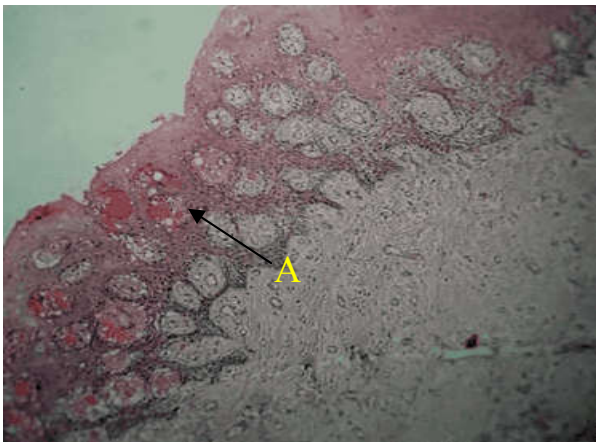

Figure 9. A-Hyperplastic epithelium with underlying dense, fibrous stroma consisting of inflammatory cells

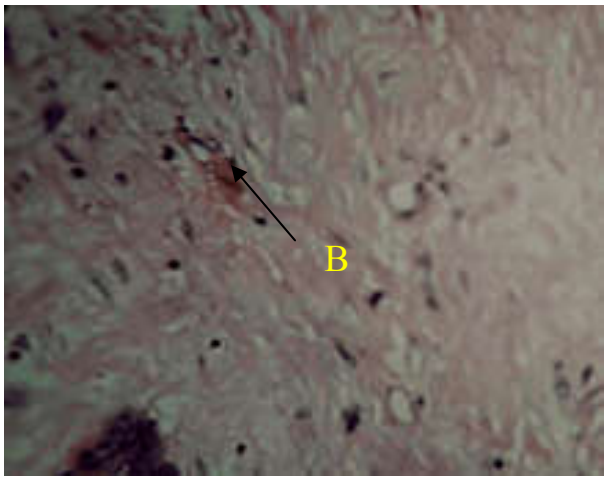

Figure 10. B-Collagen bundles with plump fibroblasts

Histologically, tissue of gingival overgrowth showed proliferation of fibers with numerous plump fibroblasts with vesicular nucleus and minimal cytoplasm. Collagen fibers were arranged in dense bundles. (Figure 2-B) In areas increased vascularity and chronic inflammatory cell infiltrate was seen in the edematous background. Overlying epithelium was parakeratinized stratified squamous epithelium of varying thickness, suggestive of Fibrous hyperplasia (Figure 1-A).

Conclusion

Drug induced gingival enlargement is the most common cause of gingival enlargement in children. Literature search reveals several case reports in this regard but in the present case there was presence of extensive gingival enlargement with the history of Cerebral Palsy coupled with Cleft lip and palate and behavioral concerns which posed a challenge and was opted

for treatment under General anesthesia. In drug induced gingival enlargement the possibility of drug replacements as suggested by the Neurophysician plays an important role along with regular follow up visits and oral hygiene maintenance.

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