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Unusual Clinical Presentation of Generalized Gingival Enlargement – A Report of 3 Cases

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ABSTRACT

Gingival hyperplasia is an aesthetically disfiguring condition causing psychological & masticatory disturbance of the oral cavity. There are wide varieties of causes of gingival enlargement ranging from most common causes like plaque accumulation, poor oral hygiene to serious systemic illnesses including blood dyscrasias, syndromes & side effects of several drugs. Here we report a case series of a neoplastic, a syndrome associated & a drug induced gingival enlargement along with a concise review on various etiologies, pathogeneses of gingival enlargement & an emphasis on the multidisciplinary approach required for the management of such distressing & functionally compromising gingival pathologies.

Keywords: Gingival enlargement, Chronic Myeloid Leukemia, Zimmermann–Laband syndrome, Nifedipine

Introduction

Gingival enlargement (GE) is defined as an abnormal overgrowth of gingival tissues. As the GE is not merely due to increase in number or size of cells but due to inflammatory component as well, the term "gingival overgrowth" or "gingival enlargement" is preferred over hyperplasia & hypertrophy.[1,2] GE is an unusual condition causing aesthetic, functional, & psychological disturbance in an individual. It may be easy for a dentist to arrive at a clinical diagnosis of GE if the cause is clearly evident, but at times it becomes necessary to seek medical advice to explore the cause and identify the underlying diseases, drug interactions or the natural body changes & to develop an effective treatment plan. When the exact cause cannot be elucidated, it becomes challenging to the dentist to establish an accurate diagnosis. We report 3 cases of aesthetically disfiguring GE, where all the three seem to have a varying etiology.

CASE 1:

A 48 years old female presented with a complaint of gradual enlargement of the entire upper & lower gums since 3 years. The enlargement was so extensive that it interfered with her speech, mastication & mouth closure. She also reported of bad breath & occasional bleeding of gums. She was a known hypertensive, receiving 20 mg of Nifedipine twice daily since 2 years. Patient had a convex profile with open bite and incompetent lips

with nodular masses of gingiva protruding between the teeth (Figure 1). Intra-oral examination revealed of bulbous, fibrotic enlargement of gingiva showing cobble stone appearance & areas of gingival inflammation. Two third portions of almost all the teeth crowns were covered with growing gums with resultant displacement of teeth & midline shift (Figure 2). On the panoramic view all complement of teeth was present with moderate amount of interdental bone loss & increased spacing between the teeth was seen. A clinical diagnosis of combined effect of drug induced (Nifedipine) & inflammatory GE was given.

CASE 2:

A 17 year old girl reported with a complaint of gum enlargement since 4 years of age. She gave a history of few embedded milk teeth in the gums which were surgically extracted at the age of 6 years. Even the permanent teeth were covered by the overgrowing gums soon after their eruption making it difficult for her to maintain her oral hygiene. Surgical exposure of all anterior teeth was done 11 years back but it recurred. She also presented with delayed milestones, challenged speech & hearing since childhood. Her medical records revealed of a single episode of epileptic attack 1 ½ years back for which she was on sodium valproate since then. Her parents had consanguineous marriage.

On examination, she was well oriented & cooperative. She had a short stature with short & stout fingers & toes (Figure 3), mild facial hypertrichosis, depressed nasal bridge, thick lips & a nodular iatrogenic scar on the right lower lip (Figure 4). On intra oral examination, there was generalized irregular fibrotic enlargement of gingiva covering two third of most of the teeth with areas of inflammation, resultant displacement of teeth & midline shift (Figure 5). Second & third molars in all the quadrants were not clinically visible. However on the panoramic radiograph, full complement of teeth was present with mild interdental bone loss & increased spacing between the teeth. Provisional diagnosis of generalized GE associated with an unidentified syndrome was given.

CASE 3:

A 46 years old male, a known case of chronic myeloid leukemia reported with gum enlargement since 2 months. He noticed an increase in the size of his gums after removal of decayed lower right & left back teeth. There was associated pain of gums while chewing & severe bleeding while brushing. He was not able to maintain a good oral hygiene. He was diagnosed with Chronic Myeloid Leukemia (CML) (blast crisis) 2½ years back & was on Tab Imatinib since then. He had mild Bell's palsy on left side of face (Figure 6). Intra orally, there was presence of generalized erythematous bulbous GE with spontaneous bleeding & exudate from gums (Figure 7). His oral hygiene was poor. Panoramic view showed moderate interdental bone loss & increased spacing between the teeth with no bone changes. Clinical diagnosis of leukemia induced GE was made.

Discussion

Various causes of GE can be grouped as follows: 1) Inflammatory, 2) Medication-induced, 3) Idiopathic gingival fibromatosis (hereditary/syndrome associated), 4) Systemic causes of GE, 5) False GE (underlying osseous lesions, dental tissues) & 6) Others (mouth breathers). GE can be inflammatory or fibrotic in nature. Inflammatory GE is the most common & is completely reversible in otherwise healthy

individuals if the local causative agent, microbial plaque; is regularly & effectively removed by mechanical teeth - cleaning procedures. Hereditary, drug related, & syndrome associated GE are usually fibrotic in nature.[2,3] Oral prophylaxis alone will not be sufficient to control the fibrotic gingival overgrowth, but even surgical excision of hyperplastic tissues is essential.

GE can be localized or generalized. Initially it may involve just the papillary & marginal portion of gingiva but may slowly progress to involve the attached gingiva; if the causative factor is still persisting. GE can also be present as discrete forms either as pedunculated or sessile masses.

GE can be graded by three methods – Cast method[4], Photographic method[5,6] & Clinical measurement method[2,7]. The scoring for GE is given by many authors, but the most accepted one is given by Bokenkamp[8] in 1994 as – Grade 0 – no signs of enlargements; Grade 1 – enlargement confined to interdental papilla; Grade 2 – enlargement involves papilla & marginal gingiva; Grade 3 – enlargement covering three quarters or more of the crown.

1) Inflammatory GE

Inflammatory GE may result from chronic or acute changes. Chronic inflammatory GE is caused by prolonged exposure to dental plaque, chronic irritation due to improper restorative & orthodontic appliances, or mouth breathing habit. Initially, life-preserver shaped enlargement is seen in marginal gingiva. It slowly increases in size & involves the papilla. Gingiva is soft, friable & deep red in colour with increased tendency to bleed. This can be treated by removal of local factors with scaling & root planing after which the gingiva shrinks & becomes firm. The persisting soft GE even after the conventional therapy is best treated by gingivectomy while the persisting firm GE is best treated by flap surgery. Acute inflammatory enlargement is usually in the form of gingival & periodontal abscess. Gingival abscess is a purulent infection involving marginal or interdental gingiva which is mainly caused by bacteria that are carried deep into the tissues by tooth brush bristles or orthodontic appliances. Initially it begins as a small red painful swelling with smooth/shiny surface. In 24 - 48 hours, swelling becomes fluctuant & pointed. If allowed to progress, it will rupture spontaneously with release of purulent discharge. Periodontal abscess is caused due to the extension of infection from pocket into supporting periodontal tissues which results in gingival swelling with presence of deep pocket & affected tooth can be depressed into the socket. Pus may drain through sulcus (or) orifice. Diffuse gingival/periodontal abscess are preferably managed through drainage along the sulcus along with removal of the etiological agent but when abscess is pointed then vertical stab incision & drainage is preferred followed by systemic antibiotics & NSAID's depending on patient's condition.

2) Medication induced GE

The three main groups of drugs that cause GE are anticonvulsants, immunosuppressants, & calcium channel blockers.[1,2,9] Theoretically, all the drugs of these groups can cause gingival overgrowth, but few drugs like phenytoin sodium (50%), cyclosporine (30%), nifedipine (10%),[2] are associated with high prevalence of overgrowths. Apart from these drugs, some authors[2] have reported overgrowths after long term use of erythromycin for tuberculosis. Among the anti-convulsants, phenytoin is the most common drug associated with GE & its incidence rate ranges from 0 - 89%.[10,11,12] It is commercially available as Dilantin Sodium. Kinball[13] was the first to report a case of Phenytoin induced GE. Other anticonvulsants associated with overgrowth are carbamazepine, primidone, phenobarbital,

ethosuximide, methosuximide, valproic acid.[1] Minimal plasma level needed for seizure control is 10 - 20µg/ml & minimal concentration of drug needed to produce overgrowth is higher than this concentration.[14] It usually starts after 3 - 6 months of therapy depending upon the periodontal status & may reach maximum in 9 - 18 months.[15] Among the immunosuppressants, cyclosporine is more often associated with gingival overgrowth.[1,2] To maintain immunosuppression, oral therapeutic dose of 10 – 20mg/kg body weight/day is required. It will result in a serum concentration of 100 – 400ng/ml. Investigations by Daley et al (1986),[16] found that all patients taking more than 700 mg of cyclosporine per day displayed at least mild GE & suggested a "threshold" dose exists above which GE occurs. Overall incidence of cyclosporine induced GE is 25% to 81%.[17] The major side effect of cyclosporine is nephrotoxicity & hypertension.[2] To counteract these side effects, usually nifedipine is given. This combination in turn increases the severity of gingival overgrowth.[8] Calcium channel - blocking agents are used extensively for the management of cardiovascular conditions & hypertension. Nifedipine is the most prescribed pharmacologic agent in this group & was the first documented to be associated with GE in 1984.[18] The onset of GE usually becomes clinically apparent within two months following initiation of therapy with nifedipine. Incidence rate of nifedipine induced GE is around 15% – 21%.[2] Other calcium channel blockers that cause GEs are Verapamil, Diltiazem, & Amlodipine.[1,2]

Drug induced gingival overgrowth starts as a bead like fibrotic generalized papillary enlargement & involves the attached gingiva in later stages. Enlargement create pesudopocket resulting in plaque accumulation giving a clinical picture of combined enlargement (fibrous & inflammatory). Withdrawal or substitution of the offending medication is the prime treatment choice but it should be considered after discussing with the patient's general physician. It has been documented that nifedipine induced GE may be reduced within one week upon discontinuation of the drug.[2] Furthermore, once drug induced GE sets in; it usually does not respond well to plaque control thus requiring surgical excision of hyperplastic tissues. The patient should be motivated to maintain strict plaque control regimen following the periodontal surgery, including regular professional cleaning then the hyperplastic gingival lesions may not recur inspite of continuation of drug.[2]

In the first case reported here, the patient had inflammatory GE to begin with, due to poor oral hygiene. The gingival overgrowth became severe when she was started on calcium channel blocker (Nifedipine), 2 years back for the treatment of hypertension, due to the unwanted effects of the drug. Hence the clinical diagnosis of combined effect of drug induced (Nifedipine) & inflammatory GE was made for this case.

The mechanism of pathogenesis of GE is an enigma that has intrigued researchers for decades. Several hypotheses have been proposed by different investigators on the mechanisms of drug induced GE. Seymour et al[19,20] in their review on the pathogenesis of drug induced gingival overgrowth; consider it as a multifactorial model; involving an interaction of several factors like the age, gender, genetic predisposition, pharmacokinetic variables, drug interactions, & periodontal status.

1. <u>Age & gender</u> – GEs are seen in any age groups depending on the drug intake. Children, teenagers are at increased risk of developing phenytoin induced GE as epilepsy is more prevalent in this age group, middle & older age group individuals are prone for GE secondary to calcium channel blockers & cyclosporine induced GE is seen in all age groups. Gender & age are not important risk factors, however males are three times as likely to

develop drug induced gingival overgrowth, & age is inversely correlated.[2,20,21,22,23]

2. Genetic Predisposition - Not all patients taking phenytoin, cyclosporine or a calcium channel blocker develop GE. Following mechanisms were put forward to explain the genetic basis:-

1) **P-450-gene polymorphism:-** All the above drugs are metabolized in liver by cytochrome p-450 group of enzyme. Genetic polymorphism in p-450 gene will result in altered metabolic activity of these drugs resulting in gum enlargement.[20]

2) **HLA-polymorphism:-** patients who express HLA-DR-1 show protection against cyclosporine overgrowth & patients who express HLA-DR–2 are susceptible to develop cyclosporine overgrowth,[24] however a different school of thought was proposed saying - examination of tissue typing data in transplant recipients has shown that HLA-B37 positive patients are significantly more likely to show severe GE, whereas the opposite is true about HLA-DR-1 positive patients.[2]

3) **Fibroblasts heterogenicity:-** phenytoin & its major metabolite 5-(4-hydroxyphenyl)-5-phenylhydantoin (4-HPPH) react with phenotypically distinct subpopulation of gingival fibroblasts & cause an increase in protein synthesis & cell proliferation rate.[19]

4) **Macrophage phenotypes:-** Responders usually contain different phenotypic macrophages which produce proliferative cytokines, resulting in alteration of connective tissue metabolism.[25]

3. Pharmacokinetics of drugs **-** It would seem that certain threshold concentrations of the drug or its metabolite is necessary to activate gingival fibroblasts or to alter connective tissue homeostasis, but this concentration may vary markedly between patients. Some studies suggest that whole blood & salivary concentrations of the drug are important determinants in the expression of gingival overgrowth[2,16,26,27] others have failed to substantiate these findings.[2,22,28]

4. Drug interactions - Interactions between simultaneously administered medications affecting GE have also been reported. Chronic co-medication with phenytoin & other anticonvulsant agents does not affect the degree of GE in adult epileptic patients.[2] However, cyclosporine treated patients are often on prednisolone or azathioprine as well, which can modify the severity of GE.[2] On the other hand, patients on cyclosporine A, who are also receiving a calcium channel blocker present with a greater severity of the gingival lesions than patients medicated with cyclosporine alone.[2]

5. Periodontal variable **-** Even though gingival overgrowth can occur in absence of plaque, presence of plaque & gingival inflammation appears to exacerbate the severity of enlargement.

Although drug induced GE has been extensively studied, the pathogenesis of this disorder has not been clarified to date. To explain this, several mechanisms were put forward –

a) Role of growth factor - It has been suggested that healthy gingiva is in a continuous state of wound repair due to constant insult from bacterial plaque & that growth factor may play an important role in this reparative or maintenance process. Thus one might expect to find cells in normal gingiva producing growth factors associated with wound healing such as platelet-derived growth factor B chain (PDGF-B). One might also expect to find increased numbers of these cells or increased amounts of these growth factors in conditions which involve increased tissue volume such as drug induced gingival overgrowth. Such growth factors are obvious targets for drugs & their activation may be important in the pathogenesis of drug induced gingival overgrowth.[2,19]

b) Inflammation from plaque - Oral prophylaxis & good oral hygiene reduces the severity & recurrence rate after excision of gingival overgrowth. This highlights the role of inflammatory mediators as follows-

- Patient with phenytoin therapy show increase number of langerhans cells which in turn is related to increase in Interleukin – 1 (IL-1) & Tumour Necrosis Factor (TNF) – α. This induces a dose dependent stimulation of Prostaglandin E_2 in fibroblasts resulting in increase in fibroblastic proliferation in presence of primary growth factors.[29]
- Cyclosporine upregulates IL - 6 expressions. IL – 6 appear to target gingival connective tissue cells both by enhanced proliferation & by positive regulation of collagen & glycosaminoglycan synthesis.[1]
- Also cyclosporine, nifedipine, phenytoin were found to synergize with IL – β to further enhance secretion of this cytokine by gingival fibroblasts in vitro there by resulting in increased collagenous protein synthesis.[30]

c) Drug - induced Alterations in Gingival Connective Tissue Homeostasis - the connective tissue in phenytoin overgrowth has a significantly higher volume density of non-collagenous matrix than of collagenous matrix.[28] A further investigation into the tissue contents of proteoglycans & glycosaminoglycans has confirmed this finding.[2] The effect of cyclosporine & nifedipine on non-collagenous matrix has been investigated with respect to 'H-glucosamine utilisation.[2] Fibroblasts obtained from a patient with gingival overgrowth secondary to both nifedipine & cyclosporine therapy metabolised 'H-glycosamine differentially from those exposed to cyclosporine in vitro & normal gingival fibroblasts. Extrapolation of these results to the in vivo situation would suggest that both cyclosporine & nifedipine can cause increased tissue level of non-sulphated glycosaminoglycans.

d) Immunoglobulins - immunological reaction mediated by T-cells may play a role in pathogenesis.[28] Aarli (1976)[31] reported that phenytoin induces significant increase in both salivary IgA levels & the IgA rate by parotid gland.

e) Collagenase activation - In vitro studies, showed that phenytoin induced GE may be more related to a lack of collagen breakdown as opposed to an increase in collagen production.[2]

f) Gingival fibroblast phenotypes - Phenytoin reacts with some of phenotypically distinct sub-population of gingival fibroblasts & resultant clinical picture is a reference of such population[32]

g) Description of fibroblast cellular Na^+ Ca^{+2} function - All three groups of drugs influence the Ca^{+2} /Na^+ flux. Inhibition of Ca^{+2} intake by fibroblasts may be correlated with the rate of fibroblastic proliferation & overgrowth.[33]

h) Folic acid - is involved in the synthesis of purines & pyrimidines which are necessary for DNA synthesis. Folic acid is also required for the activation of collagenase. This folic acid taken up by cells through Na^+ - coupled, Na^+ - dependent active transport. Phenytoin interferes with Ca^+/Na^+ transport at cellular level, resulting in decreased uptake of folic acid. High doses of folic acid (IV) gives protection against phenytoin overgrowth.[34] It was explained by:

1. Close structural resemblance between folic acid & phenytoin. Folic acid could act as competitive antagonist.
2. Folic acid – decrease the metabolite of phenytoin resulting in decrease in severity & incidence of enlargement.
3. Folic acid binds to plaque – derived endotoxin & prevents stimulation of endotoxin complement immune system. This will decrease local hyperplastic changes

i) Combination hypothesis - Combination of several factors like the drug intake, periodontal status & tooth - sulcular epithelial integrity is also responsible for gingival overgrowth.

In the second case reported here, the 17 year old girl presented with gingival overgrowth since childhood which affected both her primary & permanent teeth, the cause for which was not known. Even though the patient was on anticonvulsant for 1 ½ years at the time of presentation, drug induced GE was not considered, as the primary cause for childhood presentation was not known. Several complications of sodium valproate are known[35] but GE as a potential side effect was discussed only in very few case reports. Several authors implicated the role of mast cells in the pathogenesis of GE due to sodium valproate.[4] In contrary, the effect of sodium valproate on the periodontal & oral health of epileptic patients has been carried out in few prospective studies which showed no unwanted effects on oral & dental health.[4,36]

3) Idiopathic gingival fibromatosis

Idiopathic gingival fibromatosis is a rare hereditary condition that has no definite cause.[37,38] This condition may manifest as an autosomal dominant or, less commonly, an autosomal recessive mode of inheritance, either as an isolated disorder or as part of a syndrome. Autosomal dominant forms of gingival fibromatosis are usually nonsyndromic. Idiopathic gingival fibromatosis is a gradually progressive benign enlargement that affects the marginal, interdental, & attached gingiva. The fibromatosis may potentially cover the exposed tooth surfaces, thereby hampering the functioning of the stomatognathic system. The gingival tissues are usually pink & non-hemorrhagic & have a firm, fibrotic consistency. The autosomal dominant form is often associated with hypertrichosis, corneal dystrophy, nail defects, deafness, & craniofacial deformities. Children suffering from autosomal dominant form may suffer from mental retardation & epilepsy. In autosomal recessive form facial anomalies with hypertelorism have been observed but most forms are without defects, other than GE. Consanguinity has been observed in recessive form.[39]

Genetic conditions often present at birth (all are rare conditions) & which are associated with hereditary fibromatosis include I-cell disease, mucopolysaccharidoses, fucosidosis, aspartyl glucosaminuria, Pfeiffer's syndrome, infantile systemic hyalinosis, & primary amyloidosis. Those which cause localised GE include Fabry's syndrome, Cowden's syndrome, tuberous sclerosis, Sturge - Weber angiomatosis & gingival granular cell tumor.

Hereditary Gingival Fibromatosis (HGF) is rare, affecting only one in 7,50,000 people.[40] Gingival Fibromatosis is most commonly associated with hypertrichosis with or without mental retardation.[41] Syndromes such as Murray–Puretic–Drescher (juvenile hyaline fibromatosis) present with multiple hyaline fibromas, osteolysis of terminal phalanges, recurrent infection, stunted growth & premature death. Cross syndrome presents with microphalmia, mental retardation, athetosis, & hypopigmentation. Ruthufard syndrome is associated with corneal dystrophy. Jones syndrome presents with progressive deafness.[42] Zimmermann–Laband syndrome is characterized by abnormalities of the nose &/or ears, absence &/or hyperplasia of the nails or terminal phalanges of the hands & feet, hyperextensibility of joints, hepatosplenomegaly, mild hirsutism, & mental retardation.[43] The condition results from autosomal dominant inheritance & involves a highly variable phenotype.[43]

The interesting feature in the third case presented here was that the patient was short statured girl with short, stout fingers & toes, with mild facial hypertrichosis. She also had delayed milestones. Her parents had a consanguineous marriage. Considering all these features, we found it appropriate to give a clinical diagnosis as

idiopathic or syndrome associated GE & all these clinical features presented by patient fits into the description of Zimmermann–Laband syndrome. However our patient did not present with hepato or splenomegaly but she was suffering from epilepsy. Zimmermann–Laband syndrome associated with epilepsy has not been reported so far. Hence identification of the genetic pathways & mechanisms of Zimmermann–Laband syndrome will be useful in clarifying this disorder. In the present case, GE began when the patient was less than 1 year old, & she had gingivectomy & gingivoplasty at 6 years. But the GE recurred again to greater extent by 17 years of age. The timing of gingivectomy & gingivoplasty for gingival fibromatosis patients is controversial. According to several authors, the ideal time is when all permanent dentition has erupted, because the risk of recurrence is higher before this. Growth may worsen through adolescence, suggesting the influence of sex hormones.[43] In some cases, delay in surgical treatment may lead to deciduous dentition retention, alveolar bone resorption, mastication difficulties, disadvantageous esthetic & phonation effects, & psychological problems.[43] For the patient in this study, the local & psychological benefits & risk of recurrence were considered & early treatment was suggested.

4) Systemic causes of GE

Systemic causes of GE may be further classified as conditioned enlargement (hormonal, nutritional, allergic, nonspecific enlargement – pyogenic granuloma) & enlargement secondary to systemic diseases (leukemia, granulomatous diseases)

A. Conditioned enlargement

Hormonal - Hormonal changes occurring during pregnancy & puberty, however, have long been known to be associated with varying types of GE. Hormonal changes can significantly potentiate the effects of local irritants on gingival connective tissue.[44] Enlargement in puberty occurs in both male & female adolescents & appear in areas of plaque accumulation. After puberty the enlargement undergoes spontaneous reduction but does not disappear until plaque & calculus are removed. Incidence of gingivitis in pregnancy varies from around 50% to 100%.[45] Pregnancy does not alter healthy gingiva; it affects the severity of previously inflamed area. Kornman & Loesch (1980)[46] have reported that the subgingival flora changes to a more anaerobic flora as pregnancy progresses. "Prevotella intermedia" is the only microorganism that increases significantly during pregnancy. They also stated that the increase is due to elevations of levels of systemic estradiol & progesterone, which, by the end of the third trimester, reach levels ten & thirty times the levels during the menstrual cycle, respectively. It is generally accepted that increase in gingival inflammation typically begins in the second month & reach the maximal level during the eighth month of pregnancy.[44] This altered gingival tissue response to plaque is due to depression of the maternal T-lymphocyte.[47] These inflammatory changes may lead to gingiva that appears oedematous, hyperplastic & erythematous. The changes may be localized or generalized, & are usually noted on the marginal gingiva & interdental papilla, prevalence rate being 10% according to Butter (1987),[48] & 70% according to Ziskin (1933)[49] respectively. In some cases the inflamed gingiva forms a discrete mass referred to as pregnancy tumor. It is non - neoplastic enlargement that usually appears during first or second trimester. Its incidence is 1.8% - 5%. Pregnancy does not cause the condition, but the altered tissue metabolism in pregnancy accentuates the response to local irritants.[44] Therefore, the maintenance of oral hygiene before & during pregnancy is very important in order to reduce the incidence & the severity of gingival inflammation. Lesions that do not cause significant functional or esthetic problems should

not be excised during pregnancy because, first, they may reoccur &, secondly they may resolve spontaneously post-partum.[44]

Nutritional - Enlargement of the gingiva is generally included in classic description of scurvy but incidence of occurrence of scurvy is rare in the present generation population. Acute vitamin C deficiency itself does not cause gingival inflammation, but it causes hemorrhage, collagen degeneration & oedema of the gingival connective tissue. These changes modify the response of the gingiva to plaque to the extent that the normal delimiting reaction is inhibited & the extent of inflammation is exaggerated resulting in the massive GE. Enlargement of marginal gingiva is usually seen with gingiva appearing bluish red, soft & friable & has a smooth shiny surface. Spontaneous bleeding on slight provocation, hemorrhagic areas & surface necrosis with pseudomembrane formation are common features.

Allergic - Plasma cell gingivitis (Synonyms: Atypical gingivitis, Plasma cell gingivostomatitis) is considered to be an allergic response or hypersensitivity reaction to some component of chewing gum, dentifrices or diet. It is commonly seen in young females. It is associated with burning sensation, intense hyperaemia & oedema of free & interdental gingival. Patient usually gives a history of shifting to new toothpaste / oral rinse or chewing gum. Identification of allergic agent & removal from diet / ideally use is the first treatment strategy along with scaling & root planning.

Nonspecific enlargement – Pyogenic granuloma is a non - neoplastic inflammatory hyperplasia of skin & oral cavity. Various etiologic factors such as chronic low - grade local irritation, trauma, hormonal changes, certain drugs, bone marrow transplant, & reactions to grafts have shown to induce its initiation. The most common intraoral site is the gingiva (nearly 75%), but it also affects the lips, mucosa, & tongue. The size of the lesion usually ranges between 0.5 cm – 2 cm, & they may grow at an alarming rate reaching that size in just 4 - 7 days. There are 2 types of Pyogenic granuloma - Lobular capillary hemangioma (LCH) sessile form (66%) & Non – LCH pedunculated form (77%).[50] Bright red / purple in colour with a friable (or) firm consistency & bleeds on slight provocation. Sometimes growth may involute spontaneously on its own. The lesion is treated by removal of irritating factor like calculus, root stumps, overhanging restorations, followed by surgical excision of lesion. Recurrence rate is around 15%.[50]

B. <u>Enlargement secondary to systemic diseases</u>

a. ***Granulomatous diseases -*** **Wegener's Granulomatosis** is a pathologic triad of necrotizing granulomas of nose, paranasal sinuses & lungs, vasculitis & glomerulonephritis. Growth is either localized / generalized. It is referred as "Over-ripened strawberry" appearance due to reddish purple colour & tendency to bleed. As it is an immunologically mediated tissue injury, corticosteroids or immunosuppressants are the drug of choice for the treatment of the disease. Other granulomatous diseases producing enlargement are: Sarcoidosis, Chrohn's disease, Merkellson – Rosenthal syndrome etc.

b. ***Neoplastic GE:*** Neoplastic enlargement consists of 8% of all oral neoplasms. The most common benign tumors that cause GE include - Fibroma, Papilloma, Peripheral giant cell granuloma etc. They are usually treated by surgical excision. Among the malignant lesions, leukemia is the most common neoplasm that produces gingival overgrowths.

Leukemia - Leukemia is a malignant neoplasm of WBC characterized by infiltration of leukemic cells in the bone marrow & other tissues. Leukemia is classified based on cell involvement as Lymphocytic, Monocytic, & Myelocytic &

based on the course of the disease as acute & chronic. Leukemic infiltration of gingiva may produce GE in these patients with a prevalence rate of 3.6%.[51] Highest incidence of GE is seen in acute monocytic leukemia (66.7%). Chronic Myeloid Leukemia (CML) is a malignancy of the myeloid line of cells in the bone marrow. The three clinical stages of CML include chronic-phase, accelerated-phase & blastic-phase. Extra-medullary involvement with myeloid cells in CML is a rare but may be seen in blastic stage. The most common sites involved with extra-medullary disease are lymph nodes (10 - 61%), bone (33 - 37%) & soft tissues (30%).[51]

Dreizen et al[52] studied the clinicopathologic & histopathologic features of leukemic gingival & cutaneous infiltrates in 1,076 adults hospitalized for cancer chemotherapy but found no cases of gingival involvement with CML, thus making the case reported in this article particularly interesting. To the best of our knowledge, this case reported by us is the first report of bimaxillary aggressive GE as the presenting feature of CML. Imatinib is the drug of choice in treatment of CML. Imatinib is the first member of a new class of agents that act by specifically inhibiting a certain enzyme that is characteristic of a particular cancer cell. Usage of Imatinib has no side effects on gingiva or oral tissues.

5) False GE:

They relate to apparent increase in the size of gingiva due to increase in size of underlying osseous & dental tissues. Gum enlargement due to underlying osseous lesions like Tori, exostosis, Fibrous dysplasia, Central cysts, Central neoplasms (Neurofibroma, Hemangioma, Neurilemmoma, squamous cell carcinoma etc.) & gum enlargement due to underlying dental tissues like at time of eruption of teeth, or "Developmental enlargement" due to superimposition of bulk of gingiva on the normal prominence of enamel.

Conclusion

Eventhough generalized GE can result from multiple causes, the clinical manifestation appear similar in many cases. Identification of the cause usually poses no great challenge to the clinicians, provided they have thorough knowledge regarding those causative conditions. Rarely, diagnosis becomes difficult when associated with syndromes or has unusual pattern of presentation. Moreover, the esthetic disfigurement & the functional impairment resulting from severe gingival overgrowth can have a negative impact in the physical social & emotional well - being of the patient. This article puts an effort in highlighting the various causes & pathogeneses of GE & an emphasis on the multidisciplinary approach required for the management of such distressing & aesthetically & functionally compromising gingival pathologies.

Conflict of interest: None to declare.

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Legends of Pictures

Case 1

Figure 1

Figure 1 – Extra oral examination showing convex profile of teeth with open bite and incompetent lips with nodular masses of gingiva seen between the protruded teeth.

Figure 2

Figure 2 - Bulbous, fibrotic enlargement of both maxillary and mandibular gingiva with cobble stone appearance superadded with inflammatory components as well. Two third portions of almost all the teeth crowns covering with growing gums with resultant displacement of the teeth and a midline shift.

Case 2

Figure 3

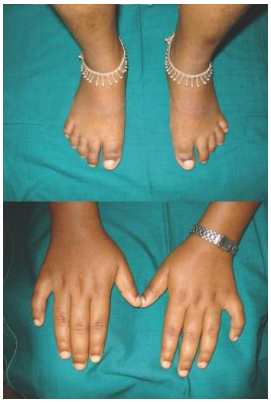

Figure 3 – Short and stout fingers and toes.

Figure 4

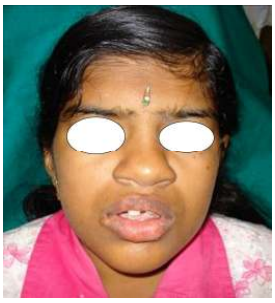

Figure 4 – Facial examination revealed mild hypertrichosis, depressed nasal bridge and a nodular scar on the right lower lip.

Figure 5

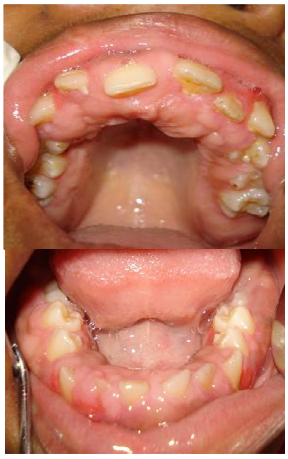

Figure 5 - Maxillary and mandibular gingiva covering two third of most of the teeth with resultant displacement of the teeth and a midline shift with areas of inflammation and erythema of gingiva

Case 3

Figure 6

Figure 6 - Patient with CML presenting with mild Bell's palsy on left side of face.

Figure 7

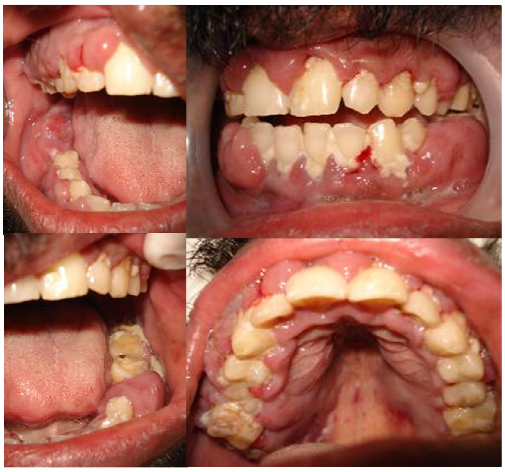

Figure 7 – Generalized erythematous bulbous gingival enlargement of both upper and lower arches with spontaneous bleeding and exudate from gums