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Severe drug-induced gingival enlargement and periodontitis: A case series with clinical presentation and management

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ABSTRACT

Gingival enlargement (GE) is a condition in which the size of the gingiva increases in response to inflammation, systemic disease, or certain medications including anticonvulsants, calcium-channel blockers, and immunosuppressants. This report describes the management of two cases involving severe gingival enlargement related to the use of an anti-hypertensive calcium-channel blocker and an immunosuppressant. Besides taking amlodipine, one patient had undergone a heart transplantation seven years prior and has been taking two immunosuppressant drugs, mycophenolate and tacrolimus. The extent of the destruction of periodontal support, aggravated by gingival enlargement, resulted in extensive tooth loss. Periodontitis and gingival enlargement exacerbate and accelerate one another and can result in loss of the entire dentition, severely affecting function and esthetics. The pharmacologic etiology sometimes cannot be altered and the patient has to be carefully managed and maintained with periodontal therapy. Physicians and dentists should be aware of these medications and be able to identify early changes in the oral cavity and to prevent, diagnose, and successfully manage the unwanted side effects of these drugs in patients.

1. Introduction

Gingival enlargement (GE) is a condition in which the size of the gingiva increases, which can be caused by inflammation, systemic disease, or certain medications [1]. Three classes of drugs known to cause GE are anticonvulsants, anti-hypertensives (specifically calcium-channel blockers), and immunosuppressants [2,3]. In patients presenting with periodontitis and gingival enlargement the conditions seem to exacerbate and accelerate one another [4]. The causative drug regimen sometimes cannot be altered as it is essential for maintenance of the patient's health. Such patients require special care and maintenance.

Amlodipine is an antihypertensive medication belonging to the calcium-channel blocker category whose primary mechanism of action involves inducing relaxation of the smooth muscle of the blood vessels and increasing their diameter, thus reducing blood pressure. In addition to gingival enlargement, side effects include fatigue, pruritus, nausea, peripheral edema, and pulmonary edema [5].

Tacrolimus is an immunosuppressant agent belonging to the calcineurin inhibitor category. It is used for organ rejection

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prophylaxis following transplantation. Calcineurin increases the activity of genes coding for IL-2 and related cytokines. However, this process is blocked by a protein complex that is created when tacrolimus binds to it and immunophilin. In addition to gingival enlargement, side effects include increased risk of bacterial, fungal, and viral infections, cardiac damage, hypertension, and a range of psychiatric conditions [5]. Presence of plaque and poor oral hygiene increase the incidence of gingival enlargement.

Mycophenolate is an immunosuppressant agent used for organ rejection prophylaxis following transplantation. Its mechanism of action is exerted by blocking de novo purine synthesis. Both B- and T-lymphocytes rely exclusively on de novo purine synthesis whereas most other cells can rely on purine nucleotide salvage. Thus, mycophenolate somewhat selectively inhibits B- and T-cells. In addition to gingival enlargement, side effects include hypertension, peripheral edema, hypotension, skin rash, easy bruising, hyperglycemia and effects on other endocrine functions, liver and hepatic dysfunction, and increased risk of infection.

2. Clinical presentation

This report describes two cases with severe gingival enlargement in the maxilla and mandible, both involving use of the calcium channel blocker amlodipine, and in one patient also involving the two immunosuppressant drugs he is taking.

Patient A is a 52-year-old African American male with a history of hypertension, diabetes and a cardiac transplant. His chief complaint was “My dentist told me my heart medication was making my gums overgrow and now I have this large overgrowth”. He had undergone a heart transplant seven years prior and has since been taking two immunosuppressant drugs, mycophenolate mofetil (2 mg 2x/day) and tacrolimus (2 mg 2x/day), both of which he will take indefinitely for maintenance of the transplant. His other medications included amlodipine (10 mg 1x/day), atorvastatin (40 mg 1x/day), carvedilol (6.25 mg 2x/day), aspirin (81mg 1x/day), insulin aspart (6–10 units 3x/day), insulin glargine (60 units 1x/day), ferrous sulfate (325 mg 3x/day) and cholecalciferol (2000 IU).

He reported pre-existing periodontal disease that had been sporadically maintained over the last seven years since the cardiac transplant. Clinical examination revealed probing pocket depths of 1–15mm and clinical attachment loss ranging from 0 to 13mm, class II-III furcation involvement (Glickman) of all first and second molars, and generalized mobility ranging from Class I-III (Fig. 1). Radiographic examination revealed generalized severe horizontal bone loss, with tooth #31 having completely exfoliated from the alveolar process. Generalized heavy sub- and supra-gingival calculus deposits and furcation involvement of all molars were noted (Fig. 2). Following the clinical and radiographic examination, he was diagnosed with Generalized Severe Chronic Periodontitis (Stage IV Grade C) and severe gingival enlargment [6]. The entire maxillary dentition and tooth #31 were deemed hopeless. The patient gave oral and written consent for treatment.

Patient B is a 50-year-old African American female with a history of hypertension, anemia, a heart murmur, and GERD. Her chief complaint was “My gums have really blown up over the last month. I can’t really chew anymore. It’s not bad pain, but constant”. Her medications included amlodipine (10mg 1x/day), as well as omeprazole (40mg 1x/day) and ferrous sulfate (325 mg 1x/day). Clinical examination revealed probing pocket depths of 3–14mm, with clinical attachment loss ranging from 0 to 8mm and generalized tooth mobility ranging from Class I-III (Miller) (Fig. 3). A complete charting of all the dentition was not possible due to pain, gingival overgrowth, and severe migration of her teeth. The panoramic radiograph showed generalized severe horizontal bone loss, with teeth #26 and #31 having completely exfoliated from the alveolar process and furcation involvement of all the molars (Fig. 4). Following the clinical and radiographic examination, she was diagnosed with Generalized Severe Chronic Periodontitis (Stage IV Grade C) and severe gingival enlargement [6]. The entire maxillary and mandibular dentition was deemed hopeless. The patient gave oral and

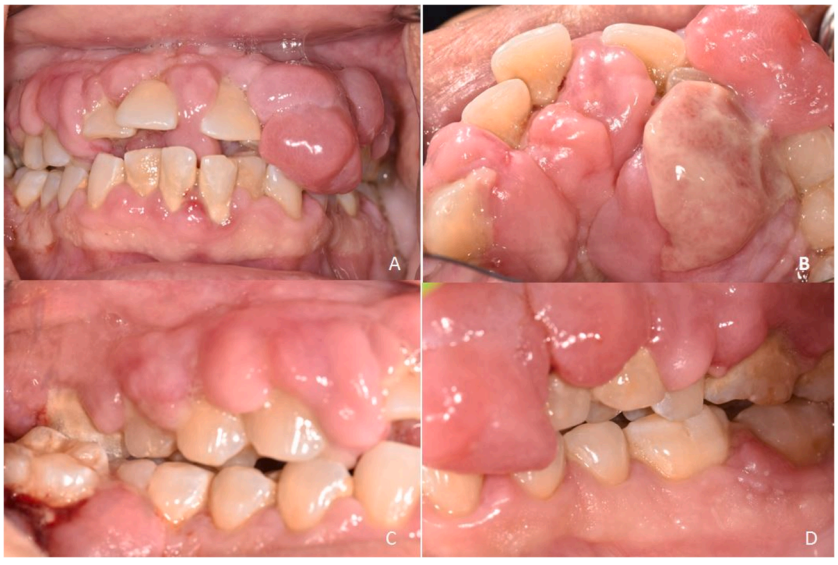

Fig. 1. Patient A: Intraoral photographs: (A) anterior view, (B) maxillary anterior palatal view, (C) lower right posterior buccal aspect, (D) lower left posterior buccal aspect.

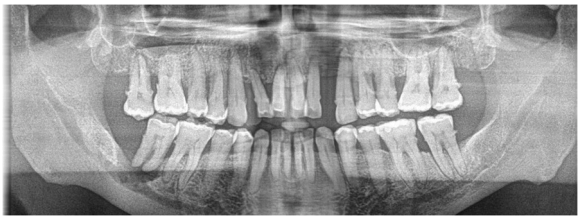

Fig. 2. Patient A: Panoramic radiograph showing generalized, severe bone loss.

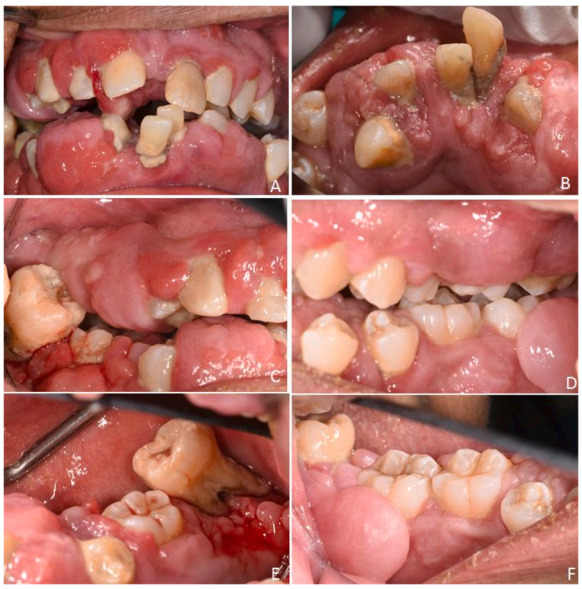

Fig. 3. Patient B: Intraoral photographs: (A) anterior view, (B) occlusal view of mandibular teeth, (C, D) buccal views of right and left sides and (E, F) lingual views of right and left side.

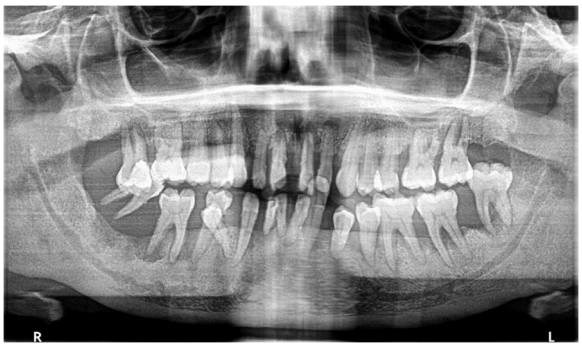

Fig. 4. Patient B: Panoramic radiograph showing generalized, severe bone loss and exfoliation of teeth #26 and #31.

written consent for treatment.

3. Case management

The treatment for patient A included extraction of all the maxillary teeth except for #3 and #15, which were kept temporarily to maintain the vertical dimension of the occlusion during healing (Figs. 2 and 5). The mandibular teeth were less severely affected by both the periodontitis and GE, and thus were able to be treated with scaling and root planning, along with extraction of #31 and localized radical gingivectomy, followed by supportive periodontal therapy (Fig. 6). Fig. 6 shows the histology. The use of tacrolimus could not be altered as it is essential for maintenance of the patient's heart transplant. The treatment plan included subsequent

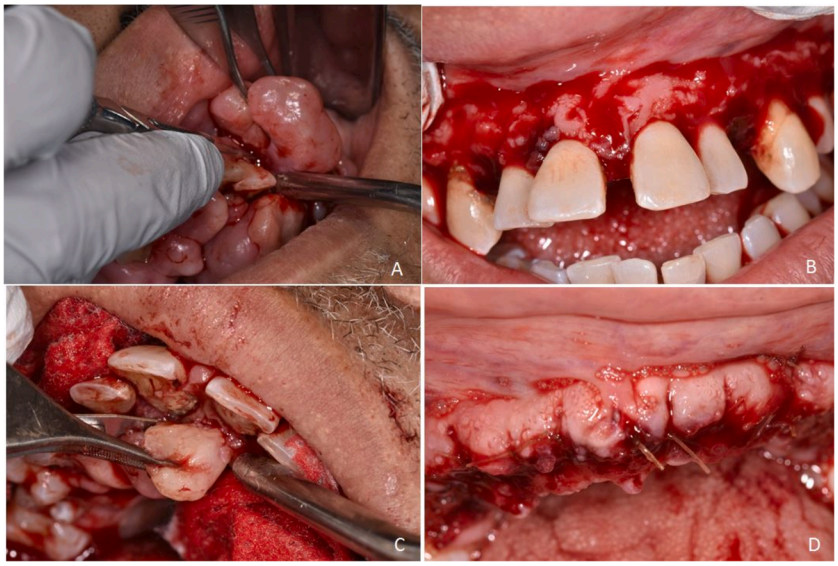

Fig. 5. Patient A: (A-C) Intraoperative photographs showing management of the maxillary gingivectomy and extractions. (D) Intraoperative photograph showing sutured edentulous maxillary alveolar ridge.

construction of a full maxillary denture.

The treatment plan for patient B included full mouth extractions and radical gingivectomy. A maxillary complete denture and an implant retained mandibular overdenture were planned to restore the patient's function. Medical consultation was submitted, with a request to change the class of antihypertensive drug, if possible.

3.1. Surgical procedure

Under local anesthesia, a reverse bevel incision was performed externally to remove the excessive gingiva. The incisions around the teeth planned for extraction were placed intrasulcularly and connected (Figs. 5 and 7). Full thickness mucoperiosteal flaps were elevated extending bilaterally. All teeth were extracted atraumatically and the alveolar ridges were reduced and reshaped as indicated by the prosthetic treatment plan. Tension-free approximation of the buccal and lingual flaps was achieved with chromic gut sutures (Figs. 5 and 7).

4. Clinical outcomes

Healing in both cases was favorable. Patient A achieved a stable periodontal status for the mandibular dentition and is satisfied with the function and esthetics of his maxillary prosthesis. (Fig. 8C and D). With elimination of the severely periodontally involved teeth and local plaque retentive factors, along with appropriate plaque control and supportive periodontal therapy, his prognosis has been improved and gingival enlargement has not recurred. Patient B is edentulous and is undergoing rehabilitation to restore function and esthetics of the maxilla and the mandible. (Fig. 9C and D). Both patients will be monitored regularly and any recurrence of gingival enlargement around the mandibular teeth for Patient A should be detected and treated in the early stage.

5. Discussion

Despite their pharmacological diversity, the two major drugs causing gingival enlargement in these patients (calcium channel blockers and immunosuppressants) are believed to have a similar mechanism of action – inhibiting intracellular calcium ion influx resulting in a common side effect upon the gingival connective tissue [7]. Gingival enlargement has been reported with all three classes of calcium channel blockers [8]. Significant gingival overgrowth has been observed in 6.3% of subjects taking nifedipine and its severity was found to be related to the amount of gingival inflammation [9]. The occurrence of gingival enlargement with use of amlodipine is less frequent and at a daily dose of 5 mg or less it causes only mild (<1/3 clinical crown) gingival overgrowth in 3.3% of the subjects [10]. Both patients is this report were prescribed a 10 mg daily dose of amlodipine and their extensive involvement with severe gingival overgrowth may be related to the higher dose.

Besides amlodipine, patient A has been taking two immunosuppressant medications implicated in causing gingival overgrowth. Tacrolimus has been used as an alternative to cyclosporin because it causes less gingival overgrowth [11]. The prevalence of gingival overgrowth in kidney transplant patients taking mycophenolate is reportedly decreased compared to other immunosuppressants and it is considered protective against such overgrowth [12]. However, the severity of the condition in patient A would seem to indicate a synergistic or modifying effect among the medications.

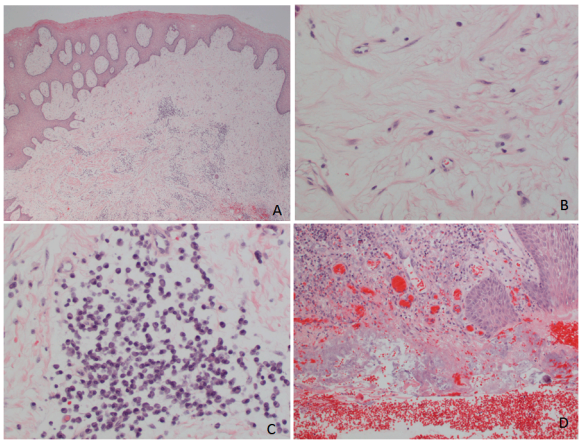

Fig. 6. Patient A: (A) Histopathology of the biopsied tissue specimen (hematoxylin and eosin stain, low power), (B) high power view of connective tissue stroma, (C) area of chronic inflammation and (D) area of ulceration.

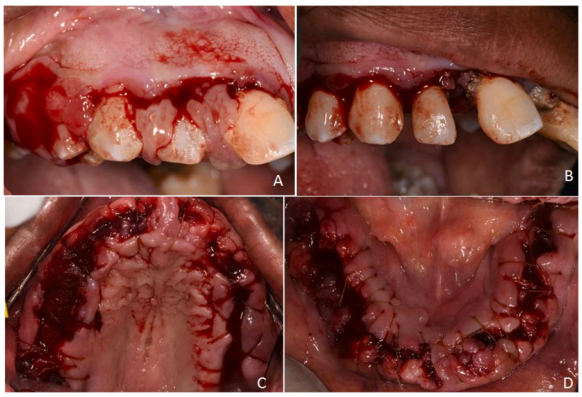

Fig. 7. Patient B: (A, B) Intraoperative photographs showing the management of the maxillary gingivectomy, (C, D) Maxillary and mandibular ridges following extraction of the teeth.

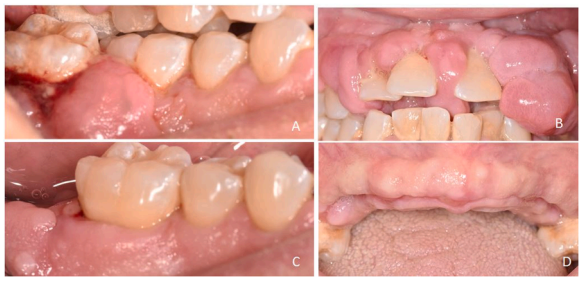

Fig. 8. Patient A: Four week postoperative photographs showing initial condition and favorable healing and stable gingival tissue in the mandible (A, C) and maxilla (B, D).

In patients presenting with periodontitis and gingival enlargement, these conditions exacerbate and accelerate one another [4]. High plaque scores and gingival inflammation are important etiologic factors in exacerbating drug-induced gingival enlargement irrespective of the causative medication. Patients with significant gingival enlargement have been observed to have greater plaque scores and papillary bleeding indices [9,13]. The patients described in this report presented with generalized heavy calculus deposits, considerable plaque and unmanaged periodontal disease. The severity of gingival enlargement in patients taking these medications correlates with poor plaque control and is commensurate with the degree of plaque-induced inflammation. Good plaque control and regular periodontal maintenance are important in the management of patients taking these medications.

Tooth movement and displacement in these cases can be attributed to an active force provided by the gingival overgrowth along

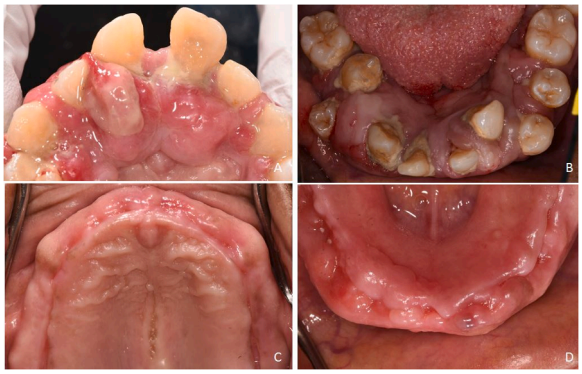

Fig. 9. Patient B: Maxillary (A) and mandibular (B) dentition and soft tissues at initial examination compared to favorable healing one month following treatment (C, D).

with an undetermined factor of alveolar remodeling [14]. The force mechanism is unknown, but could be related to increased gingival collagen production by the fibroblasts [15]. The tissues in gingival overgrowth exhibit a thickened connective tissue stroma accompanied by the increased presence of collagen fibers, thickened epithelium, and elongated rete pegs. Histologic analysis of the specimen from patient A showed these characteristics (Fig. 6). There was also a significantly higher numbers of basement membrane disruptions, a discontinuous collagen type IV expression pattern and decreased laminin 5 [16].

Medication-related gingival enlargement generally requires intervention. Surgical treatment is often the main treatment option for patients with severe overgrowth. Physicians and dentists should be aware of these medications and be able to identify early gingival changes once medication has been started. Patients under the regular care of a dentist may benefit from early detection of gingival tissue changes, when non-surgical techniques can then be used to reduce the extent of plaque-induced gingival inflammation and limit the occurrence, or reduce the rate of recurrence, of this unwanted side effect and devastating tooth loss [17].

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