Case Report

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Nonsurgical and Surgical Approach for Management of Cyclosporine-A and Nifedipine-Induced Gingival Overgrowth

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KEYWORDS

Gingival overgrowth, Drug-Induced, Cyclosporine, Nifedipine, Immunosuppressive medication, Calcium channel blockers

ABSTRACT

Gingival overgrowth (GO) is primarily a result of plaque-induced inflammatory process. However, GO is a modified inflammatory response due to predisposing factors such as systemic diseases or medications used by patients. GO is an established side effect related to some medications and hence referred to as medication-induced or drug-induced gingival overgrowth (DIGO). Over the past half a century, there has been an increasing trend in reporting of DIGO. The three main groups of predisposing medications for DIGO are anticonvulsants, immune-suppressants and calcium channel blockers. Among the calcium channel blockers, nifedipine is commonly used in the management of hypertension and other cardiovascular diseases. Immunosuppressive medication, cyclosporine-A is often prescribed for patients receiving organ transplants. When these predisposing medications are prescribed singly or in combination, there is an increased risk of DIGO as a clinical manifestation. A definitive diagnosis is important in the successful management of such patients. Timely diagnosis and effective dental care oriented for preventive and early therapeutic interventions would help in preventing serious complications with functional, aesthetic and systemic implications for the patient. Close collaboration with the medical and dental teams would invariably support the notion of integrated care tailored for specific treatment needs identified in these patients.

INTRODUCTION

Gingival overgrowth (GO) is the enlargement of gingival tissue in its mass and volume. Although GO is primarily instigated by plaque-induced inflammatory process, the inflammation can be exaggerated by predisposing medications used by a patient. GO related to medications is referred to as 'medication-induced' or 'drug-induced' gingival overgrowth (DIGO). Such medications may act as potential risk factors, predisposing the susceptible individuals for DIGO.

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The three main groups of predisposing medications for GO are, anticonvulsants, immune-suppressants and calcium channel blockers. Calcium channel blockers such as nifedipine, amlodipine and felodipine are used for the treatment of cardiovascular diseases. Nifedipine is widely used in the management of hypertension, angina and cardiac arrythmias. Immunosuppressive medications are often prescribed for patients receiving organ transplants. This is to prevent long-term rejection of the transplant. Cyclosporine-A has proven to be a promising immunosuppressant for organ recipients, and those with relatively untreatable autoimmune diseases [1]. However, as reported by Rateitschak-Pliiss et al [2], cyclosporine-A could elicit GO in organ-transplanted patients.

Supposedly, cyclosporine-A shares a close relationship with DIGO, with reported incidence of 25-30% [1]. Similarly, nifedipine and amlodipine,

the commonly used antihypertensive medications reveal their incidences as 20% and 7% respectively [3-5].

For the last half a century, the incidence pattern of DIGO appears to vary between different medications or groups of medications. However, the clinical manifestation of DIGO remains the same or even escalated. Therefore, increasing attention is focused on this pharmacologically-influenced oral complication.

While GO is a medication-induced side effect, it is primarily manifested in individuals who fail to maintain optimal standards in plaque control. In patients with GO, chronic inflammatory changes are apparent during the clinical examination. The diagnosis is usually based on patient's history of predisposing-medications and poor oral hygiene status.

Histologically, an increase in the gingival epithelial thickness is commonly seen DIGO, with an increase in mitotic activity, especially in the spinous cell layer of oral epithelium [6]. The gingival connective tissue shows collagen fibrosis, increase of vascularity, infiltration of inflammatory cells containing plasma cells and lymphocytes [7,8]. It is hypothesized that an imbalance in collagen metabolism and abnormal differentiation of fibroblasts result in their accumulation with proliferative and synthetic phenotypes [9].

While DIGO may appear in any part of the mouth, anterior gingivae appear to be a commoner site, where interdental papilla and attached gingivae are usually involved. As reported in the literature, no data provides a convincing answer for why anterior gingivae are more often affected by GO than posterior gingivae [1]. Similarly, buccal gingivae are commonly affected than the lingual or palatal gingivae [10]. Although the exact pathogenic mechanism of DIGO and the factors governing its site predilection is not understood yet, it could be hypothesized that differential proportions of subsets of fibroblasts may exist in different anatomical locations in the mouth and the susceptible individuals may demonstrate an exaggerated inflammatory response to dental plaque accordingly. Site predilection may also be related to less voluminous nature of the interdental papillae of the posterior gingivae with a wider area of interdental col, when compared to more voluminous papillae in the anterior gingivae with a narrower interdental col area.

The median time of onset of DIGO with immunosuppressants, calcium channel blockers and anticonvulsants are reported to be 71, 262 and 37 days, respectively [11]. As the tissues enlarge with time, the overgrown tissue may extend coronally, covering a significant portion of the clinical crown. This may challenge oral hygiene maintenance as well as aesthetics of affected patients.

CASE REPORT

Patient description with case history

A 19-year-old female presented to a Periodontology specialist clinic complaining gradual enlargement of her gums for the past one year. Medical history revealed that she is a kidney transplant recipient 10 years ago, and currently on prophylactic medications and iron and vitamin supplements, prescribed by her nephrologist and transplant surgeon. She was continuing oral cyclosporin-A 50mg morning and 75mg at night, mycophenolate mofetil 500mg twice daily, nifedipine 20mg twice daily, prednisolone 10mg every other day, and vitamin B complex daily, folic acid 1mg daily and FeSO4 200mg daily. The patient had no previous experience of dental treatment. Oral hygiene practices were, twice-daily brushing with a manual toothbrush and fluoridated toothpaste. No parafunctional habits were evident. She was unemployed, a non-smoker, with no habit of alcohol consumption and belonged to a low-income family.

Clinical Examination

Extra-orally, normal facial profile with competent lips was observed.

Intra-orally, all teeth, except maxillary third molars were clinically present. However, mandibular third molars were partially erupted. Slight attrition of lower right central incisor (41) was evident. Bilateral cross-bites of the canine regions with moderate crowding around lower canine to first premolar regions were also evident.

Oral mucosa appeared normal in colour and texture. Gingivae was pale pink with significant enlargement of the upper and lower anterior segments (Figure 1.1,1.2,1.4). Lower labial gingiva was the most affected with moderate to severe gingival overgrowth, especially involving the interdental papillae, covering about half of the clinical crowns of incisors. However, lower posterior buccal gingivae, on both sides were minimally affected, with no apparent GO, except slight gingival swelling. Lingually, the lower gingiva

was free of overgrowth, except localized swelling and false pocketing of mesio-lingually inclined 44 and 45 with moderate crowding of 44, 43 and 42 (Figure 1.4).

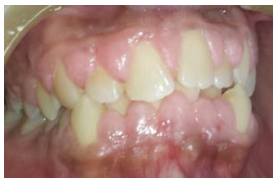

Figure 1.1 Front view

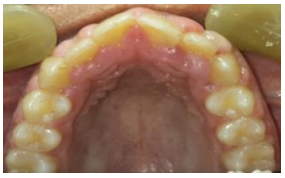

Figure 1.3 Upper arch

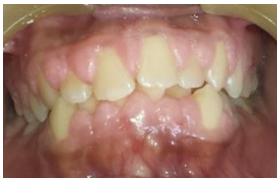

Figure 1.2 Lateral view

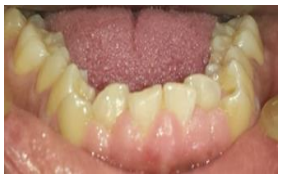

Figure 1.4 Lower arch

Upper anterior labial segment showed moderate gingival enlargement extending from canine to canine. However, GO of upper posterior teeth was slight and less pronounced, extending from premolar to molar region on both sides (Figure 1.1, 1.2). The palatal aspect of the gingivae was almost free of GO, both in anterior and posterior parts, yet with localized gingival swelling visible on the palatal aspect of 12 and 13 (Figure 1.3).

The overgrown tissue on both upper and lower gingivae were soft and fibrous in consistency. Periodontal assessment revealed the plaque score (PLS) of 68%, bleeding score (BS) of 25%, with no evidence of true periodontal pockets or loss of attachment. Increased probing depths of 4-5mm evident in most of the areas with mild to moderate gingival enlargement. A few sites were 6-7mm deep, but detected as false pockets localized to lingual aspect of 44 and 45 (Figure 2.1). There was no tooth mobility. Based on the clinical picture, periodontitis was excluded from the provisional diagnosis. However, her oral hygiene was suboptimal.

Results of Investigations

DPT radiograph revealed intact periodontal support with no apparent bone loss. Horizontally-impacted 48, vertically impacted 38, 28 and 18 were noted. Radio-opaque superimpositions were noted in the crowded lower canine-premolar region bilaterally (Figure 2.2).

Excisional biopsy was performed during the surgical resection of the gingival overgrowth of upper and lower anterior segments (Figure 3.1). Histopathological findings revealed parakeratinized stratified squamous epithelium and the corium with increased amount of fibrous connective tissue with increased vascularity (Figure 2.3, 2.4, 2.5). Chronic inflammatory infiltrate was not much evident. It concluded the histopathological diagnosis as 'drug-induced gingival hyperplasia'.

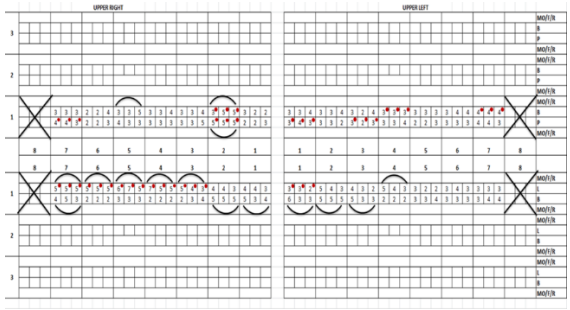

Figure 2.1 Detailed Six-Point-Pocket Chart

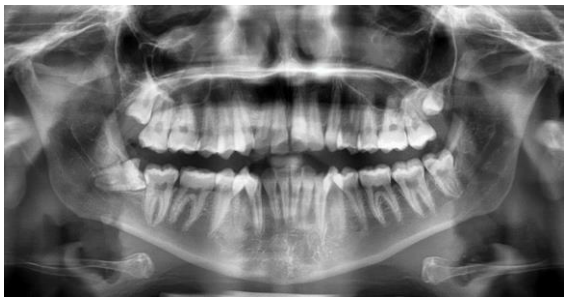

Figure 2.2 DPT

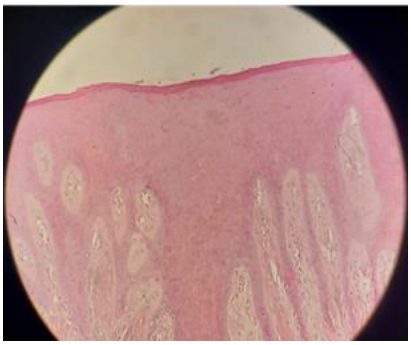

Figure 2.3 The epithelium consists of parakeratinized stratified squamous epithelium (Staining: H&E; Magnification:20x)

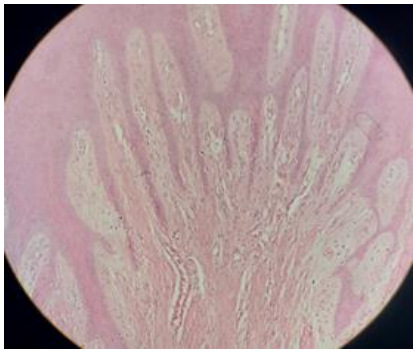

Figure 2.4 The corium which exhibits an increased amount of fibrous connective tissue and increased vascularity. (Staining: H&E; Magnification:20x)

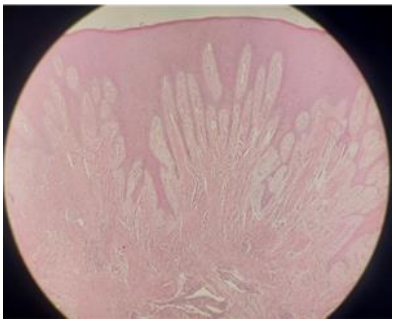

Figure 2.5 The corium which exhibits an increased amount of fibrous connective tissue and increased vascularity. (Staining: H&E; Magnification:10x)

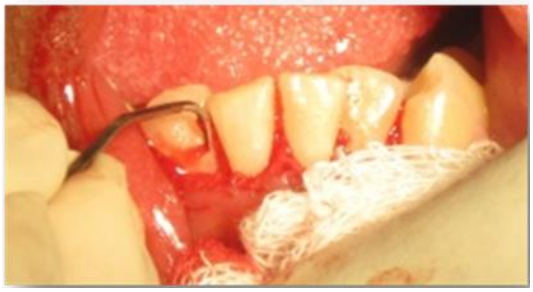

Figure 3.1 Gingivectomy of lower arch

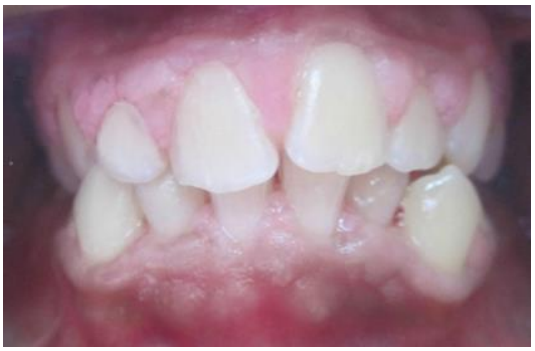

Figure 3.2 Post-operative review

Diagnosis

Primary diagnosis of this case was "chronic generalized, moderate gingivitis with cyclosporin- & nifedipine-induced gingival overgrowth".

Additional diagnoses were:

- Bilaterally impacted upper and lower third molars,
- Lower anterior moderate tooth crowding with bilateral cross-bite of upper and lower canines

Treatment Plan

After a discussion with the patient, the following treatment plan was designed:

1. Patient motivation and oral hygiene education (OHE) with information on how the gingival condition is affected due to suboptimal plaque control and reaction to the related medications
2. Liasing with patient's medical practitioner (nephrologist) for medical advice during periodontal treatment
3. Non-surgical periodontal care with professional mechanical plaque removal (PMPR), under the recommendations received from the nephrologist
4. Introduction of interdental cleaning aids (interdental toothbrush, and single-tufted toothbrush)
5. Periodic review (in every two weeks to assess oral hygiene with full mouth plaque scores and bleeding scores, reinforce oral hygiene education and perform further PMPR as necessary)
6. Gingivectomy surgery, if the overgrowth is not regressing, provided the patient achieves an optimal plaque control (under the advice from the nephrologist)
7. Post-operative review following gingivectomy surgery
8. Supportive Periodontal Care (SPC)
9. Surgical referral for partially-erupted/impacted 38 and 48
10. Orthodontic referral for management of cross-bite and crowding, provided the patient achieves a stable periodontal condition.

Treatment

The initial visits were dedicated for thorough oral hygiene instructions (OHI). The patient was informed of the details of her periodontal condition and recommended periodontal management. Detailed explanation was given on the importance of oral hygiene maintenance and how it would help in preventing GO.

Next, the patient was referred to her nephrologist with a written-referral. The purpose was to seek advice regarding the precautionary measures prior to periodontal treatment, especially with the potential gingivectomy surgery indicated in the plan. According to the nephrologist's recommendation, precautionary measures were taken to minimize the chances of oral infection. Invasive treatment procedures were performed under prophylactic antibiotic cover. Amoxicillin 2g was administered orally, prior to the invasive procedures. Subsequently, based on the nephrologist's recommendation, amoxicillin 500mg three times per day was continued for 5 days post-operatively.

At the following visits, nonsurgical periodontal therapy (NSPT) was performed with thorough PMPR in two sittings. OHI were reinforced, especially for interdental cleaning with interdental-

and single-tufted toothbrushes. Single-tufted toothbrush was specifically recommended to be used around the gingival margin of teeth with crowding (42, 43, 44) and to access the posterior teeth with partially-erupted mandibular 3rd molars.

At the 4-week review after NSPT, patient's oral hygiene status was evaluated. She was found to be engaging with adequate plaque control, with a PLS of 29% and BS of 18%. However, OHI were reinforced, and another full-mouth PMPR was performed.

The next review appointment was arranged 2-weeks later. Further reduced PLS (15%) and BS (6%) were noted. The patient appeared to have sustained reasonable level of motivation in maintaining oral hygiene.

Following the above NSPT and regular monitoring of her plaque control, it was noted that the gingival overgrowth has reduced to some extent, with some reduction in false pocketing. However, GO of upper and lower anterior sextants had not regressed significantly. Therefore, it was decided to proceed with gingivectomy surgery. The patient was pre-prepared for the surgical session with explanation of its benefits and potential risks. Written consent was obtained.

Gingivectomy was performed in two-sittings each under a prophylactic dose of 2 grams of oral amoxicillin. Under local anaesthesia, overgrown gingival tissue of lower anterior sextant was removed by following the conventional gingivectomy procedure with a manual surgical blade (Figure 3.1). Surgical excision was uneventful. Resected tissue was sent for histopathological examination. At the one-week post-surgical review, satisfactory healing and oral hygiene maintenance were noted.

Within the next two weeks review period, the patient was closely monitored for oral hygiene maintenance. She was able to maintain satisfactory plaque control, with 15% PLS. 2-weeks following this short review period, gingivectomy of upper anterior sextant was carried out by following the same above protocol. One-week postsurgical review was uneventful with satisfactory healing.

At the 4-weeks post-operative review, PLS and BS were 17% and 4% respectively. Significant reduction in gingival tissue was evident. However, persistent inflammation and swelling of the papillae were noted in relation to 22, 23, 12 (Figure 3.2).

After surgical treatment, future review visits were arranged in 6-8 weekly intervals. PLS of 16% and 18% were noted at two subsequent review intervals. However, considering the susceptibility of this patient for recurrence in GO, it was decided to continue regular long-term follow-up care with shorter recall intervals, where periodic PMPR, oral hygiene reinforcement and monitoring would be carried out.

Treatment Outcome and Follow-up

The clinical evaluations after the surgical therapy showed improvement in aesthetic appearance and she was able to improve on plaque removal with the recommended tooth brushes. Although the patient was very pleased with the immediate treatment outcome, it is envisaged that persistent and recurrent gingival overgrowth is possible in this patient who appeared to be highly susceptible for GO. Since it is imperative that the patient continues her prescribed medications for the survival of the kidney transplant, she was thoroughly advised to continue medication while maintaining optimal oral hygiene. The patient is currently under stringent maintenance schedule delivered according to the supportive periodontal care (SPC) plan.

The medical management of this patient is being continued with close follow-up by the Nephrology Unit under the consultant nephrologist. According to the patient's medical records, she is continuing the same medications with slight dose adjustments from time to time. Periodic reporting to the medical clinic regarding the patient's periodontal condition, dental treatment and maintenance care is currently ongoing.

SPC was initiated with regular one-monthly recall intervals, with the aim of maintaining long-term periodontal stability, while continuing preventive and therapeutic interventions as required. So far, the patient required reinforcement of plaque control, emphasis on changing the toothbrushes as they wear-off, along with professional mechanical plaque removal (PMPR). The preventive care, close monitoring and regular PMPR benefited the patient to be free of recurrences of GO. She is also capable of maintaining good oral hygiene with low plaque levels. Under this improved oral condition, surgical removal of impacted 38 and 48, and orthodontic consultation are to be decided in the future. Further, the patient was well informed of the importance of shared medical and dental care in the long-term management of her oral and general health.

DISCUSSION

According to the current evidence, organ transplantations are on the rise. This is a result of the recent advances in medicine, enabling survival of patients with failing organs. However, the organ recipients are required to undergo treatment with multiple medications including immunosuppressants to prevent rejection of the transplant. Immunosuppressive medications are usually coupled with other medications to harmonize any adverse effects. Moreover, the compromised health and immune system of these patients place them at high risk for both systemic and oral infections. Therefore, the dental management of a graft-recipient may pose several challenges to the dental practitioner. Considering the potential complexity of dental treatment in these patients, they invariably need specialized dental care, especially when detected with oral diseases.

Cyclosporin-A, though highly effective for maintaining the transplanted organ, it has many potential side effects such as hypertension, bleeding problems, changes in liver and kidney function and poor wound healing. As a measure of mitigating these side effects, low doses of corticosteroids in combination with other immunosuppressants are usually prescribed for these patients. Concomitant use of corticosteroids with cyclosporine-A is a standard prophylaxis regimen to prevent transplant rejections.

The patient described in this case report was already on cyclosporin-A, mycophenolate mofetil, nifedipine, prednisolone, vitamin B, folic acid and iron supplements on a regular basis. Mycophenolate mofetil (MM) is an immunosuppressant which is usually combined with cyclosporine and steroids such as prednisolone. However, MM also lowers the natural immunity in these patients and carries the adverse effects of decreased white cell counts, opportunistic infections, and gastrointestinal problems.

Considering the vulnerability of these patients to experience more complications during dental treatment, prior-consultation of patient's physician is highly recommended. Premedication with prophylactic antibiotics is usually recommended for these patients prior to invasive dental procedures. The selection of appropriate regimen is done in consultation with the physician [12].

Accordingly, our patient was managed under the advice of her nephrologist, and the invasive surgical procedures were performed under prophylactic antibiotic, amoxicillin. As described under the treatment details of this patient, initial NSPT was carried out first with thorough plaque control guidance and monitoring of the progress of the patient.

This 19-year-old patient was very compliant with home-care maintenance, throughout active treatment. Therefore, significant false-pocket reduction and control of inflammatory swelling were evident, after non-surgical periodontal debridement. However, due to the high severity of GO, the overgrown tissue further persisted. Therefore, surgical resection with gingivectomy was necessary for further management of GO.

Medication induced GO appears to be more prevalent in children and adolescents [13-15]. The lower anterior region of the gingiva is the most commonly affected area, as it is more prone to plaque accumulation and inflammation [16]. Accordingly, the severity of GO can range from mild to severe, often correlating with the duration of medication use and the individual's response to the drug. This patient is an adolescent who had severe GO mainly localized to upper and lower anterior gingivae.

While the clinical appearance of GO may generally be similar across different drug-induced causes, research has shown that the gingival tissues affected by cyclosporine A (CsA) is prone to bleeding when probed compared to other drug-induced forms of GO [17]. Furthermore, the histopathological findings indicate that CsA-induced GO is highly inflamed and exhibits less fibrosis compared to GO associated with other medications. This may suggest underlying pathological processes driving CsA-induced GO differing from the mechanisms involved in other drug-induced gingival enlargement conditions. In this case, increased amount of fibrous connective tissue and increased vascularity were noted although, chronic inflammatory infiltrate was not much evident.

Moreover, our patient was on two medications (cyclosporin-A and nifedipine) which trigger GO. Therefore, notwithstanding her low plaque and bleeding scores noted at 6-8 weekly review visits, stringent follow-up supportive periodontal care was planned. This is after considering her susceptibility and the risk for development of recurrences in GO. The short recall periods enabled

us to carry out regular PMPR which also helped in preventing recurrence of GO.

As reported by O'Valle et al [18], numerous previous studies have reported a trend of increase in the incidence of GO due to simultaneous treatment with Cyclosporine-A and calcium channel blockers such as nifedipine. Other studies report that the above combination could result in more severe degree of GO [19,20]. Therefore, previous evidence appears to be conclusive in accepting the fact that administration of nifedipine further potentiates the adverse effects of cyclosporine-A.

Due to the pharmacological and biological mechanisms described in the previous sections of this case report, periodontal management of patients undergoing combined treatment of cyclosporine-A and nifedipine can be challenging. Both medical and dental practitioners have major, shared roles in combatting this health implication for patients.

In general terms, the approaches for management of gingival overgrowth include NSPT with thorough plaque control measures and PMPR where plaque and calculus are removed by scaling. If the patient is affected with periodontitis, root surface instrumentation is needed. If NSPT is insufficient in resolving GO, it may warrant surgical removal of overgrown gingival tissue. Surgical removal of GO may involve gingivectomy, gingivoplasty and flap procedures. However, the patient should receive continuous motivation and guidance from the practitioner for effective plaque control during active periodontal therapy as well as in the supportive periodontal care period. Usually, the change of medication to an alternative would be the last resort.

The key approaches for preventing recurrence of GO are multi-faceted. Previous research has consistently demonstrated that maintaining optimal oral hygiene through meticulous plaque control and regular professional prophylaxis are crucial factors in the prevention of recurrence of GO [21]. Adjunctive nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids may help in reducing inflammation and further overgrowth. However, NSAIDs cannot be given to kidney transplant recipients due to potential nephrotoxicity. According to established evidence, regular maintenance therapy, including frequent follow-up visits and monitoring allows early detection and intervention for any recurrence.

Given the patient's existing crowding in the lower arch and the cross-bite, orthodontic treatment may eventually be beneficial in terms of plaque removal ability, prevention of occlusal interferences and trauma from occlusion which may be detrimental for periodontal health in the future. However, any persistent GO could significantly complicate the orthodontic approach, since the fibrotic and hyperplastic gingival tissue associated with this condition has shown to impede tooth movement posing challenges for a desired treatment outcome [15]. Furthermore, any heightened plaque accumulation and increased risk of gingival inflammation in these patients elevate the chances of developing periodontal complications, which could further disrupt the orthodontic treatment plan [22]. Therefore, these factors are to be considered and discussed with the orthodontist at the point of referral for orthodontic consultation. If the patient is consistent in adhering to a stringent plaque control regimen, and able to remove plaque in the crowded areas of dentition, orthodontic intervention may not be required.

This case report is an important contribution to the dental literature for several reasons. GO is a well-documented side effect of CsA, a commonly used immunosuppressant drug in kidney transplant patients. Reporting such cases in a specific patient population can add insights in understanding epidemiology. Identifying the patient-specific risk factors, such as dosage and duration of CsA use, oral hygiene status, and genetic predisposition can provide valuable insights into the aetiology of GO. Detailed description of the clinical characteristics, including the extent and severity of GO may explain the clinical spectrum of this condition. Documenting the approach to the management of GO with non-surgical and surgical interventions can help establishing best practices for the oral and periodontal care of kidney transplant patients.

This case report also highlights the importance of effective communication and collaboration between the dental and medical teams in the management of these complex patients, ensuring a comprehensive and coordinated approach for care. Evaluating the short-term and long-term outcomes of the management strategies including the impact on oral health, aesthetics, function, and overall quality of life, can provide valuable insights for clinicians treating similar cases. By sharing this case report, the authors intend to contribute to the existing knowledge base, and promote delivery of evidence-based, patient-centred care for kidney transplant patients with gingival overgrowth.

CONCLUSION

Oral health maintenance is an integral part of the overall health in uplifting the quality of life of an individual. There is a strong and timely need for controlling the rapidly increasing noncommunicable diseases in the human kind, especially for chronic and life-threatening conditions such as cardiovascular diseases, seizure disorders, renal diseases, and improving the survival of organ or tissue transplants in treated cases. Therefore, continuous use of anticonvulsants, immunosuppressants and calcium channel blockers would be an indispensable part in managing the patients with serious medical conditions. In this backdrop, DIGO gains substantial attention and clinical importance for the dental practitioner. Both medical and dental practitioners should join force and follow a holistic approach in managing these patients successfully.

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DECLARATION OF INTEREST

Authors declare no conflict of interest.

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