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Post-Transplant Gingival Hyperplasia: A Brief Review

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ABSTRACT

Drug-induced gingival hyperplasia is an abnormal enlargement of the gingival tissues, which can occur as a side effect of Cyclosporine A, following renal transplantation. It is a debilitating condition, which can result in increased dental infection rates, tooth loss and subsequent reduced masticatory function. Although immunosuppressive agents such as Cyclosporine A are known to cause this oral side effect, many other medications (such as Nifedipine) and anticonvulsant (such as Phenytoin) which are not uncommonly used in renal transplant patients can exacerbate this condition. With the improving survival rates of renal transplant patients, more patients are on long-term immunosuppressive regimens and therefore we see an increase in the prevalence of gingival hyperplasia in the population. The aim of this article is to present the aetiology, pathogenesis and management of gingival hyperplasia.

INTRODUCTION

Cyclosporine (CsA) is a calcineurin inhibitor and a potent immunosuppressive agent commonly used as first-line therapy for preventing allograft rejection following renal transplantation [1]. Gingival overgrowth is one of the most commonly encountered side effects of this medication, with a prevalence of up to 70% according to studies [2]. The calcium channel blockers, mainly Nifedipine, that are used as an adjunct to treat the hypertension commonly seen in renal transplant patients can exacerbate this side effect. Other medication such as the mTOR inhibitor sirolimus, anticonvulsants such as phenytoin, and anti-metabolites such as azathioprine can also cause gingival hyperplasia. Resultantly, many patients present with inflamed, hyperplastic gingivae, which predispose them to dental decay and periodontitis, as well as increase their risk of tooth loss and reduced masticatory function. The disfigured appearance of the gingivae can also result in reduced self-esteem and psychological distress. This overgrowth is not an intended pharmacological action of the drugs; however, this side effect can negatively impact the patient's quality of life. In recent years, Tacrolimus has been shown to reduce the incidence of post-transplant rejection whilst having fewer side effects on the oral cavity [3]. The substitution of Cyclosporine for Tacrolimus, along with meticulous oral hygiene advice and dental review could help reduce the incidence of gingival hyperplasia in transplant patients. The possibility of gingival debulking surgery could also be considered as a treatment option for these patients.

CLINICAL MANIFESTATIONS

Drug-induced gingival overgrowth commonly presents within 3 months of commencing Cyclosporine treatment as enlargement of the interdental papilla [4,5]. It can extend to involve the remainder of the gingival tissues, extending apically past the mucogingival margin or coronally towards the occlusal surface. It is more commonly seen in the anterior mandible, followed by the anterior maxilla **(Figures 1a and 1b)** [6]. The tissues tend to have an erythematous appearance; however, the degree of cellularity, inflammation and fibrosis have been shown to vary according to factors such as genetics and oral hygiene [4], all of which will be discussed later in the paper.

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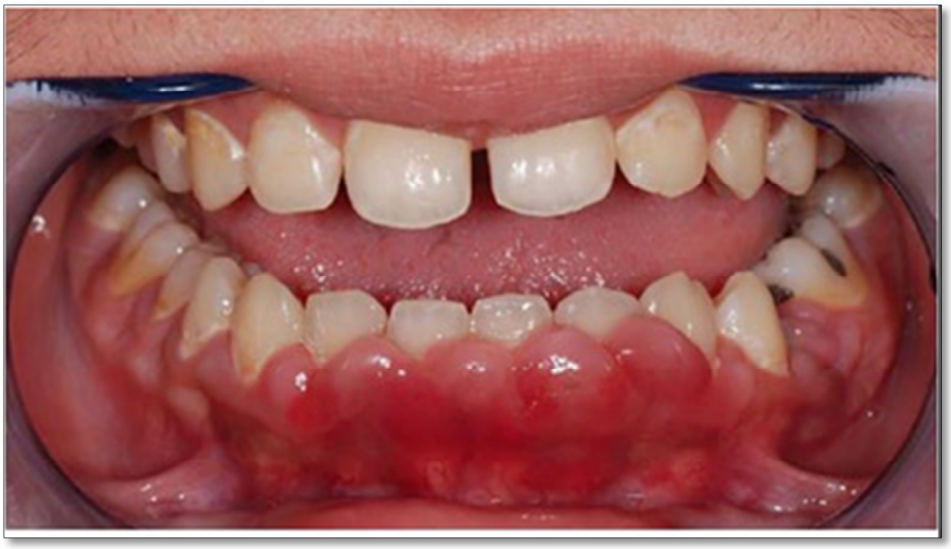

Figure 1a. Mandibular gingival hyperplasia [7].

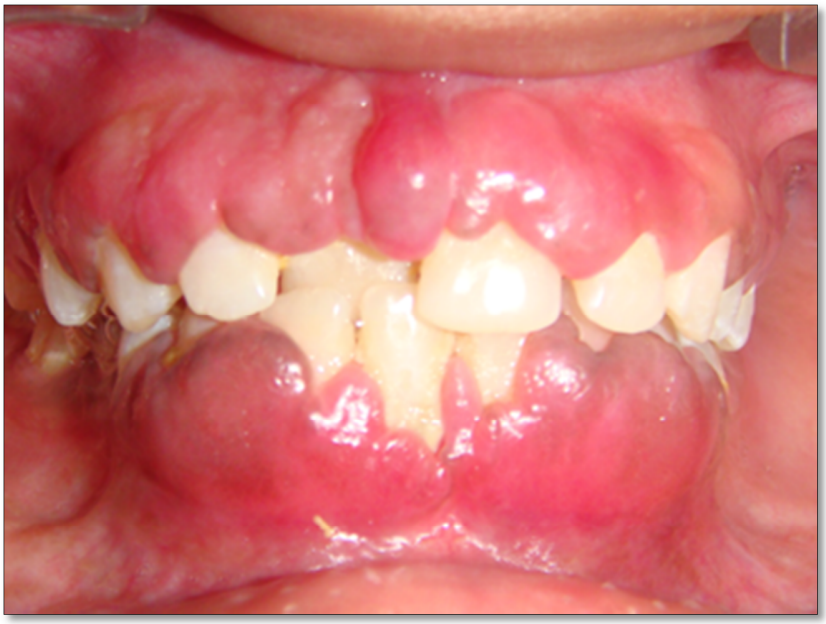

Figure 1b. Hyperplasia affecting both maxillary and mandibular labial mucosa [8].

PATHOGENESIS

The pathogenesis underlying drug-induced gingival overgrowth is not fully understood. However, it is most likely multifactorial, with a plethora of contributing hormones and cell mediators. Studies have shown that CsA, along with anti-hypertensives and anticonvulsants alter the metabolism of gingival fibroblasts, reducing the activity of lysosomal enzymes, and decreasing the phagocytosis of the gingival fibroblasts [9,10]. As a result, the apoptosis and turnover of the fibroblasts are reduced, resulting in accumulation within the gingivae. It has also been suggested that there is an overall reduction of collagenase gene expression, further reducing the degradation of gingival cells [10]. Other studies have demonstrated an increase in the prevalence of chemical mediators such as angiotensin II, endothelin-1, transforming growth factor (TGF-β), connective tissue growth factor (CTGF) as well as an insulin-like growth factor (IGF). All of these hormones resulted in the activation of gingival fibroblasts and increased fibrous tissue deposition [4]; their specific mechanisms are summarized in **Figure 2**. In all the overall conclusion of these studies is that the presence of CsA promotes fibroblast formation and reduces matrix metalloproteinase production and thus fibroblast degradation **(Figure 2)**.

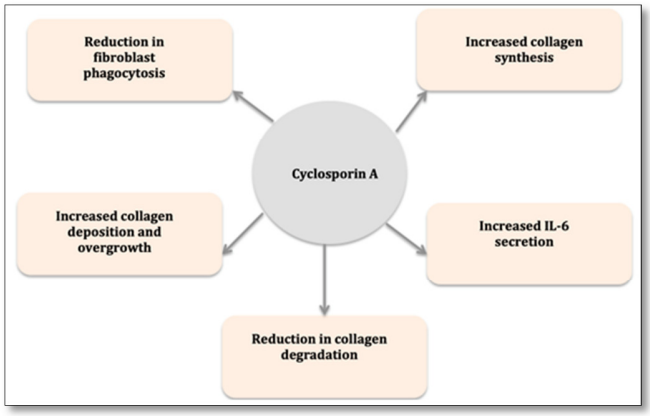

Figure 2. Suggested mechanism of CsA induced overgrowth.

In contrast to these theories, other studies have suggested that the cellular characteristics of gingival overgrowth vary according to drug type. Analysis of gingivectomy samples indicated that in the case of CsA, the overgrowth was mainly inflammatory in nature, with minimal fibrosis. In comparison, the effect of calcium channel blockers such as nifedipine resulted in overgrowth that was more fibrous in nature [11]. These findings go against the common theory that all gingival overgrowth is fibrotic in nature. In terms of Nifedipine, the samples contained higher concentrations of the fibrosis marker periostin. This was as a result of the medication causing an upregulation of TGF-β, which increased periostin expression [11]. Unfortunately, there was no clear mechanism behind the inflammatory nature of the gingival overgrowth induced by CsA, however in combination with Nifedipine, patients presented with hyperplasia of both inflammatory and fibrous origin (**Table 1**). Although these theories do not give us clear pathogenesis of gingival overgrowth, they help offer an understanding of some of the mechanisms involved behind this clinical presentation.

Table 1. The role of various cell mediators in gingival hyperplasia [11].

TGF-β	- Expression elevated in response to injury. - Induces ECM gene expression and supresses matrix metalloproteinase production.
ILGF	- Involved in the proliferation, apoptosis and differentiation of tissues. - Directly acts on fibroblasts to induce collagen production and down regulation of collagenase production.
CTGF	- Promotes syntheses of ECM. - Overexpression leads to increased fibrosis in gingival tissues.
Angiotensin II	- Up regulates TGF-β expression. - Can only induce fibrosis in the presence of TGF-β.
Endothelin-I	- Increased levels found in gingival overgrowth cases. - Modulate the synthesis of TGF-β and TNF-α, which medicate fibrosis.

RISK FACTORS

There are many factors that have been suggested to influence an individual's susceptibility to the development and severity of gingival hyperplasia. Medication dose is a controversial variable, with opinions divided regarding whether it does; in fact, affect the onset and severity [3]. Animal studies showed a significant relationship between the dose of Nifedipine and the severity of the hyperplasia; however, when combined with Cyclosporine dose showed no significant impact [1]. Although there is no clear answer to this, it is generally accepted that in order for gingival overgrowth to develop, a threshold serum concentration of causative agent needs to be reached [12]. Studies have gone on to show that gender and sex may have a part to play in susceptibility, with a reported genetic predisposition associated with HLA DR-1, HLA DR-2 and HLA-B37 genes [13]. Furthermore, adolescent females are thought to be more susceptible due to the production of a sex hormone that produces a metabolite that results in increased collagen synthesis [14].

A proven risk factor is oral hygiene. Not only does the presence of plaque initiate a local inflammatory response that results in gingival erythema and edema, but these inflammatory changes have been shown to increase the interaction between CsA and fibroblasts, resulting in proliferation4. Plaque control is paramount in reducing the severity of the overgrowth, as maintaining clean gingival tissues has been shown to reduce the overgrowth by 40% [11]. Furthermore, the presence of hyperplastic gingival tissues acts as a plaque trap and encourages bacteria accumulation, therefore patients with poor oral hygiene are not only more susceptible to developing gingival hyperplasia, but they more likely to have further increases in inflammation and overgrowth over time [3]. A longitudinal study measuring the severity of CsA induced gingival hyperplasia showed that the hyperplasia was less severe in patients with a given oral hygiene regime in comparison to those without [3].

MANAGEMENT

Non-surgical

The use of non-surgical management options should be used as first-line treatment for patients with gingival overgrowth. Not only are they the most conservative options and therefore have fewer associated risks, but they can increase the success of future surgical therapies. Ideally the most effective non-surgical management modality would be ceasing the use of CsA, however understandably this is not an option, as it would result in a drastic increase in allograft rejections following transplantation. When possible, the use of Tacrolimus as an alternative to CsA would be advised, as it has been shown to have fewer oral side effects, with only 30% of patients presenting with gingival hyperplasia [5] in comparison to the up to 70% prevalence seen with Cyclosporine [2]. This medication change may not be suitable for all patients, and therefore other non-surgical methods may need to be considered.

Due to the strong relationship between severity and oral hygiene all patients should have a thorough oral hygiene regime regardless of any other non-surgical or surgical treatment options. This regime is usually best made with the input of a dental surgeon and a dental hygienist, in order to ensure that the patient is receiving the most appropriate advice tailored to them. This regime may include regular hygienist appointments for scaling or root surface debridement [15-17]. The liaison with a dental practitioner allows the provision of multidisciplinary care and ensures that the gingival hyperplasia is being closely monitored.

The use of topical antifungal agents such as Nystatin on the enlarged interdental papilla of immunosuppressed patients has been reported to aid resolution the lesions [18]. Clinical trials have also suggested the use of systemic Azithromycin to help reduce the lesions as well as the use of non-steroidal inflammatory agents to reduce the IL-1 mediated inflammation [19]. Although these options are not suggested as being first-line options in the literature, it may be worth considering them as adjunctive treatment modalities.

Surgical

Non-surgical treatment may only reduce the severity of the hyperplastic gingiva, and therefore consideration of surgical options may be needed. When periodontal surgery is to be considered, a discussion with a restorative dental surgeon within secondary care is necessary to determine the appropriate surgical approach. Many surgical options are available, including flap surgery, gingivectomy, laser debulking and electrosurgery [5]. Consideration for the underlying bone anatomy (presence of osseous defects) the presence of active periodontitis and the gingival biotype is vital [5]. Although surgical removal of the hyperplastic tissues initially provides good outcomes, recurrence was observed in 34% of surgical cases within 18 months. Other studies have even shown recurrence within 3-6 months of surgery [5]. These factors need to be considered before embarking on surgical treatment as the unpredictable long-term improvement seen may not be worth the surgical risk and the painful post-operative recovery.

Other immunosuppressive medications and gingival hyperplasia

Although CsA is the medication that is most commonly associated with gingival hyperplasia in renal transplant patients, there are other medications that may be used that also exacerbate this condition. Tacrolimus is commonly used as a replacement therapy in cases where CsA has caused severe gingival hyperplasia as is known to have fewer oral side effects; however it is not devoid of risks. Patients receiving Tacrolimus still present with gingival overgrowth, however it is to a lesser extent (only 30% of patients) [5]. Other potent immunosuppressive medications such as the mTOR inhibitor sirolimus has been shown to also result in gingival hyperplasia, but again to a lesser extent in comparison to CsA. A study comparing the presence of gingival overgrowth in patients on different immunosuppressive regimens revealed that CsA resulted in hyperplasia in 59.1% of the sampled patients in comparison to 12.0% and 16.7% for patients treated with tacrolimus and sirolimus, respectively [20].

Interestingly anti-metabolites such as Azathioprine and Mycophenolate Mofetil (MMF) have been shown to have a protective effect, with reduced prevalence of gingival hyperplasia in patients on combination therapies rather than CsA alone. In this study a combination of CsA and Azathioprine resulted in 60.2% of cases presenting with hyperplasia and a combination of CsA and MMF resulted in 47.2% prevalence [20]. When comparing this to the 100% prevalence of gingival hyperplasia in patients receiving CsA and prednisolone not only does this indicate that Azathioprine and MMF have a protective function on the

gingiva, but it indicates that prednisolone can exacerbate the effect of CsA [20]. The respective effects of these drugs on the gingiva can be seen in **Table 2**.

Table 2. The varying effects of immunosuppressive medications/adjuncts on the gingival tissues.

Medication	Severity of Gingival Hyperplasia
Cyclosporine	+++++
Tacrolimus	++
Nifedipine	+++
Sirolimus	+++
Prednisolone	+
Azathioprine	--
MMF	---

CONCLUSION

Although drug-induced gingival hyperplasia in renal transplant patients may be unavoidable in some cases, there are non-surgical treatment modalities that can be adopted to allow patients to manage this condition. Although the histopathology and etiology are not fully understood, clinicians can agree on the importance of meticulous oral hygiene for patients. Patients should be warned of the risks of CsA and Nifedipine, as this will allow them to take the required precautions to help reduce their risk. Consideration for combination therapy using Azathioprine and MMF may help reduce the prevalence of gingival hyperplasia in transplant patients. Multi-disciplinary management of these patients is imperative in ensuring holistic patient care.

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