



## Drug-induced gingival enlargement

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### Introduction

Drug-induced gingival enlargement is classified by the American Academy of Periodontology as a dental plaque-induced gingival disease,<sup>1</sup> as evidence suggests that existing gingival inflammation may be necessary for its development and that proper plaque control and effective oral hygiene can lessen its severity or potentially prevent its occurrence altogether.<sup>2,3</sup> Currently, there are over 20 medications from three pharmaceutical categories including anticonvulsants, calcium channel blockers and immunosuppressants that are associated with gingival enlargement.<sup>4</sup> It is the responsibility of the dental practitioner to recognize the potential of these medications to contribute to gingival enlargement and to provide the proper prophylactic care or appropriately refer the patient for periodontal therapy. A team approach involving a consultation with a periodontist and the patient's physician is a critical step in successful treatment.

### Risk factors

During a course of treatment with a medication implicated in the pathogenesis of drug-induced gingival enlargement, poor plaque control is the most significant risk factor associated with its development. The severity of enlargement is often proportional to the amount of gingival inflammation present and not the dosage of medication. Overall, males tend to be affected three times as often as females<sup>5</sup> and age is inversely correlated with likelihood of occurrence.<sup>6</sup>

### Medication

Prevalence of gingival enlargement with phenytoin (Dilantin®) use has been shown to be up to 50%, while other anticonvulsants such as valproic acid, Phenobarbital® and Tegretol® have been shown to be rarely associated with the disorder. Of the calcium channel blockers, nifedipine (Adalat®, Procardia®) and diltiazem (Cardizem®) are the most likely to cause gingival enlargement (5-20%) while amlodipine (Lotrel®, Norvasc®), felodipine (Aggon®, Plendil®) and verapamil (Calan®, Covera®) are far less likely to be implicated. Cyclosporin A, an immunosuppressant commonly used in organ transplant patients, has been shown to be associated in 25-30% of adult patients and over 70% in children,<sup>6</sup> while tacrolimus has a significantly lower association at 14%.<sup>7</sup>

### Pathogenesis

While the physiology behind drug-induced gingival enlargement has not been definitively elucidated, histopathologic studies have shown that the gingival tissue volume increase is due to an excessive accumulation of extracellular matrix proteins including collagen and ground substance with a predominance of plasma cells.<sup>6</sup> Hence, the increase in tissue volume

is primarily a connective tissue response and not epithelial.<sup>8</sup> Recent evidence suggests that this overgrowth could occur not from over-production of collagen, but rather through prolonged cell life of keratinocytes.<sup>9</sup> Another hypothesis is that fibroblasts in susceptible patients are sensitive to the medication in question, causing increased protein, and hence collagen, production.<sup>10</sup>

### Clinical presentation

Clinically, gingival enlargement frequently appears within 1-3 months of the initiation of treatment with the offending medication.<sup>11</sup> The facial surfaces of the gingiva in anterior sextants are often most severely involved, and the patient may present with inflamed, fibrotic masses spreading from the interdental papillae to the attached gingiva that may interfere with mastication, speech and esthetics. Due to discomfort secondary to inflammation and the physical topography of the enlarged gingiva, oral hygiene may be impaired and diet can be adversely affected. This can lead to a host of other problems including caries, periodontal disease and immunosuppression secondary to malnutrition.<sup>6</sup>

### Treatment and prevention

Meticulous oral hygiene and plaque control combined with the removal of local factors are essential for any patient taking drugs associated with gingival enlargement. A three-month periodontal maintenance interval is strongly recommended<sup>12</sup> as well. While excellent oral hygiene and professional plaque control can potentially prevent or lessen the severity of the condition, they often are insufficient for reversing the process once established.<sup>13</sup> It is therefore prudent to consult the patient's physician to discuss potential drug substitutions that may result in regression of the lesions with proper supportive periodontal care and oral hygiene. After drug substitution or withdrawal, evidence suggests that gingival lesions may resolve in 1-8 weeks in some patients.<sup>14</sup>

In transplant patients, however, drug substitution or cessation may not be an option due to the risk of transplant rejection. Treatment of gingival enlargement in patients taking cyclosporin A should focus on their chronically immunosuppressed state. In these patients, evidence suggests that topical antifungal treatment<sup>15</sup> such as Nystatin lozenges, chlorhexidine rinses or a short course of azithromycin (3-5 days; 200-500 mg/day)<sup>16</sup> can be effective. There is evidence that systemic azithromycin remains effective in reducing gingival overgrowth from three months to two years after treatment,<sup>16</sup> but this data is controversial.<sup>17</sup> A topical treatment including scaling and root planing in conjunction with an azithromycin-containing toothpaste used twice daily for one month has been

shown to be effective in reducing gingival overgrowth as well,<sup>18</sup> but the long-term efficacy of this treatment is unclear.

If the patient has gingival overgrowth and is currently taking:	Discuss the following substitution with the primary care provider:
<b>Nifedipine</b> (6-15%)	Isradipine, Amlodipine, Verapamil, Felodipine
<b>Phenytoin</b> (50%)	Carbamazepine, Valproic Acid, Vigabatrin, Phenobarbitone
<b>Cyclosporin A</b> (Adults 25-30%, Children >70%)	Tacrolimus

Note: incidence of gingival enlargement in parentheses. Table adapted from Dongari-Bagtzoglou 2004.<sup>6</sup>

While non-surgical therapy and, if possible, drug substitutions should be attempted first, surgery is often necessary to fully correct the esthetic and functional impairment encountered in this disorder. Surgical excision has been successful in non-responding nifedipine cases when combined with good oral hygiene<sup>19</sup> as well as in cases associated with verapamil<sup>20</sup> and diltiazem, but it does tend to recur.<sup>21</sup>

A classic external bevel gingivectomy is an option to reduce redundant tissue. An internal gingivectomy approach, however, has been advocated<sup>13</sup> due to its ability to provide primary closure and reduce the incidence of postoperative bleeding, discomfort and infection. Due to its technical difficulty, this procedure may be best referred to a periodontist. Another surgical option is the CO<sub>2</sub> laser due to its decreased surgical time, rapid hemostasis and its compatibility with a host of underlying medical conditions.<sup>13</sup>

### Recurrence

Eighteen months after surgical therapy, the recurrence rate of gingival overgrowth in patients taking cyclosporin A or nifedipine was 34% in a study of 38 individuals. Age, gingival inflammation and attendance at recall visits are all significantly related to recurrence.<sup>2</sup> To help prevent recurrence postsurgically, chlorhexidine rinse twice daily is recommended.<sup>22</sup>

### Conclusion

Drug-induced gingival enlargement is a common sequela to treatment with anticonvulsants, calcium channel blockers and immunosuppressants. Evidence suggests that gingival inflammation is critical in its pathogenesis. While it may be prevented through meticulous periodontal maintenance and home care, it is essential for the dentist to work together with the patient's physician and periodontist in order to successfully treat this condition once it occurs.

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