

# Gingival Hyperplasia: Interaction between Cyclosporin A and Nifedipine?

A CASE REPORT

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**G**ingival hyperplasia, a disfiguring condition resulting in gingival tissue enlargement, is an adverse oral side effect of exposure to drugs. First documented with phenytoin,<sup>1</sup> an anticonvulsive agent, gingival hyperplasia can be elicited by other medications, including nifedipine<sup>2-5</sup> and cyclosporin A.<sup>6,7</sup> Nifedipine, a vasodilator, is used in cardiotherapy to relax cardiac vascular muscle by blocking the transmembrane flux of calcium through calcium channels. Cyclosporin A, an immunosuppressant, whose major mode of action is to inhibit the proliferation of T-lymphocytes stimulated by either antigens or mitogens, is commonly administered to patients receiving organ transplants.<sup>8,9</sup>

Gingival hyperplasia, induced either by nifedipine or cyclosporin A, is characterized by keratinization of the epithelium

covering the gingival tissue enlargement and pronounced epithelial downgrowths into the underlying collagen-laden connective tissue. Hyperplasia is most marked on the labial gingiva of the upper and lower anterior teeth. The affected areas appear as firm, nodular, granular outgrowths, with pseudopockets and marginal inflammation, as evident by excess bleeding when probed.<sup>8,9</sup> Problems associated with this condition may include poor aesthetics, eating difficulties and fetor oris.<sup>10</sup>

Combinations of these drugs

are routinely prescribed for patients who have undergone a renal transplant, because nifedipine, in addition to controlling hypertension, can reduce cyclosporin-induced nephrotoxicity. In 1987 Slavin and Taylor<sup>11</sup> observed that patients medicated with both cyclosporin A and nifedipine had more severe gingival changes than when cyclosporin A was used alone. The following case report lends further support to an intensified gingival hyperplasia in patients simultaneously administered nifedipine and cyclosporin A.

## ■ ABSTRACT ■

*Treatment with either cyclosporin A or nifedipine may induce gingival hyperplasia. A case report is presented which describes a patient medicated simulta-*

*neously with both drugs and who subsequently developed extreme hyperplasia. Could such a severe gingival pathology have resulted from an additive interaction between the two drugs?*

### Case Report

A 45-year-old African American woman complaining of excessive growth of her gums presented to the New York University College of Dentistry. This growth was noticed by the patient for about two to three years. Clinical examination revealed severe gingival hyperplasia of the maxilla and mandible. Posterior involvement was largely buccal, both on the maxilla and mandible. Eighty percent of the mandibular anterior incisors were covered with hyperplastic tissue (Figure 1) and pseudopockets of 9 mm were evident. Hyperplastic tissue was seen on both the buccal and the lingual of the mandibular incisors. Hyperplastic overgrowth was noted, although to a lesser extent, on the posterior teeth. Her medical history included renal failure, a renal transplant in 1989, and secondary hypertension; her daily medication consisted of prednisone (5 mg), immuran (75 mg), lopressor (100 mg), Lasix (40 mg), nifedipine (30 mg), and cyclosporin A (15mg, 2X).

The patient was diagnosed with gingival hyperplasia secondary to the medications, cyclosporin A and nifedipine. The treatment plan was a gingivectomy and gingivoplasty of both dental arches. Because the patient expressed extreme apprehension about the surgery, the gingivectomy was performed with the patient under sedation in the Ambulatory Surgical Unit (ASU) at Long Island College Hospital in Brooklyn, NY. A post-operative healing stent was used. The patient was taught proper home care techniques and was instructed to return for maintenance therapy every three



Figure 1. *Gingival hyperplasia of 45-year-old African American woman medicated simultaneously with cyclosporin A and nifedipine.*

months. Biopsy of the tissue showed chronic inflammation, fibrosis and hyperplasia of squamous epithelium.

### Discussion

Although it is well documented that cyclosporin A and nifedipine each independently can induce gingival overgrowth, the nature of this interaction is not well delineated. The question of defining the mode of interaction between cyclosporin A and nifedipine is twofold. First, does simultaneous exposure to cyclosporin A and nifedipine in-

crease the incidence of gingival overgrowth, that is, is there an increase in the number of patients experiencing gingival overgrowth? King et al<sup>10</sup> and Thomason et al<sup>12</sup> noted that the incidence of clinically significant gingival overgrowth in patients medicated with cyclosporin A alone was similar to that in patients receiving both cyclosporin A and nifedipine simultaneously. Conversely, Bokenkamp et al<sup>13</sup> in their survey of pediatric kidney recipients, observed an increase in the incidence of gingival hyperplasia in children receiving a combination of both drugs.

Second, does simultaneous exposure to cyclosporin A and nifedipine cause an increase in the severity of the gingival overgrowth? Again, there is controversy. King et al<sup>10</sup> observed that the cyclosporin A effect in inducing gingival hyperplasia was not potentiated by simultaneous exposure to nifedipine, whereas Thomason et al,<sup>12</sup> Bokenkamp et al<sup>13</sup> and O'Valle et al<sup>14</sup> observed that gingival overgrowth was potentiated in those patients taking the combined therapy. The severity of the gingival hyperplasia noted in

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the case reported here, as evidenced by the extreme overgrowth (>80%) and by the location on the buccal and lingual on the mandibular incisors, strongly suggests that this pathology resulted from the combined drug therapy of cyclosporin A and nifedipine.

Difficulties in interpreting the mode of interaction between cyclosporin A and nifedipine may reflect the lack of clearly defined and accepted, nonsubjective, quantitative parameters for assessing clinically obvious gingival enlargement. However, a few studies have attempted to identify specific criteria, including pharmacologic markers<sup>9</sup> and periodontal clinical parameters,<sup>10,12</sup> for evaluating gingival hyperplasia. An interesting approach to assess gingival hyperplasia, developed by O'Valle et al,<sup>14</sup> is based on the digital image analysis of photographs of the anterior regions of the upper and lower dental arches.

Because of improved patient and allograft survival rates resulting from its use, cyclosporin A is now the medication of first choice in all types of organ transplants. Hypertension in renal transplant recipients, including cyclosporin A-related hypertension, is often treated with nifedipine. About 20 percent of patients seen in specialized referral clinics are diagnosed with renal hypertension.<sup>15</sup> Since the use of cyclosporin A and nifedipine, and other calcium blockers and antagonists that also induce gingival overgrowth is expected to increase, a concurrent increase in the prevalence of gingival hyperplasia will most likely ensue. Therefore, the dental team will, most likely, encounter both more and more severe

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cases of drug-induced gingival hyperplasia in the future.

Alternate therapies should be explored. Bokenkamp et al<sup>13</sup> have recommended avoiding calcium channel blockers in the long-term management of hypertension in children receiving cyclosporin A. Other avenues of investigation are the identification of hypersusceptible populations (through a consideration of, for example, age and nutritional status) and the elucidation of clinical histories (for example, oral hygiene, dose and duration of drug treatment) that may predispose patients to gingival hyperplasia. □

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