Gingival enlargement

Gregory A. Pette, DMD, MS; Michael A. Siegel, DDS, MS, FDS RCSEd; William B. Parker, DDS

THE CHALLENGE
A 29-year-old woman visited the postgraduate periodontics clinic at the College of Dental Medicine, Nova Southeastern University, Fort Lauderdale-Davie, Fla., for a consultation in June 2009 because she was experiencing gingival enlargement. The periodontist (G.A.P.) elicited a history of grand mal epilepsy. The onset of the epilepsy occurred at the time of puberty. The patient reported having no other medical conditions. She indicated that she had four to five grand mal seizures per year coincident with her menstrual cycle. She also reported that her seizures were preceded by auras. She had been under the care of a neurologist since the onset of her epilepsy. The neurologist had prescribed a regimen of phenytoin to treat the patient’s seizures.

Before the patient sought care at the postgraduate periodontics clinic, a general dentist in private practice, who was a family friend, noted the gingival enlargement approximately five years after the onset of the seizures and encouraged the patient’s private-practice neurologist of record to perform an oral examination (Figure 1). The patient had not seen a dentist during this five-year period, so the periodontist (G.A.P.) could not ascertain whether the gingival enlargement predated the onset of the seizure disorder. The neurologist discontinued the phenytoin treatment, because it is known to cause gingival enlargement, and prescribed valproic acid. Approximately eight months after the patient ceased taking phenytoin, she visited the postgraduate periodontal clinic. The patient’s oral hygiene was poor and she had received no professional prophylaxis or deep scaling since her last dental appointment five years earlier.

Initial therapy consisted of deep scaling and root planing in four quadrants followed by the at-home use of chlorhexidine gluconate 0.12 percent for a two-week period. The periodontist re-evaluated her condition six weeks later (Figure 2). Excessive fibrotic gingival tissue remained, with mild to moderate pseudopocketing and moderate to severe loss of attachment. The periodontist performed guided tissue regeneration with a recombinant platelet-derived growth factor and beta tricalcium phosphate in the maxillary right and left posterior sextants, then performed open flap curettage with apically positioned flaps at all other sites. All periodontal surgery took place with the patient under enteral sedation with lorazepam (2 milligrams by mouth). During periodontal surgery, the periodontist removed excess gingival tissue and subsequently sent it for microscopic evaluation and interpretation (Figure 3). As of this writing, the patient is undergoing orthodontic therapy while she remains on a three-month periodontal maintenance schedule (Figure 4).

Can you make the diagnosis?

A. Drug-influenced gingival enlargement
B. Hereditary gingival enlargement
C. Leukemic infiltration
D. Tuberculosis

© 2011 American Dental Association. Republished by Medical Online Publication SAL with permission of American Dental Association. All rights reserved. JADA 2011, Volume 142, No 11, Page 1265-1268
“Drug-influenced gingival enlargement” and “drug-induced gingival overgrowth” are the preferred terms for what previously was referred to as “gingival hyperplasia,” “gingival hypertrophy,” “gingival fibromatosis” and “elephantiasis gingivae.” The medications commonly associated with drug-influenced gingival enlargement include antihypertensive agents such as the calcium channel blockers (including nifedipine, diltiazem and verapamil), as well as antiseizure medications such as phenytoin, sodium valproate, valproic acid, phenobarbital and primidone.1-13 Immunosuppressants such as cyclosporin A also are implicated in gingival enlargement. While some spontaneous resolution has been associated with discontinuing the use of certain medications such as nifedipine, this generally is not the rule.13 At this patient’s initial visit to the neurologist, she was receiving only phenytoin treatment. Therefore, her history supports a diagnosis of phenytoin-influenced gingival enlargement. However, because the gingival enlargement did not appear to improve after the elimination of the phenytoin, one also must consider sodium valproate as a cause of the drug-influenced gingival enlargement.14

The information in the patient’s medical, dental and drug histories and the clinical presentation usually are sufficient to attain a diagnosis of drug-influenced gingival enlargement; therefore, a biopsy is not necessarily mandated. However, to demonstrate such a diagnosis more definitively, a biopsy procedure certainly is preferred. The clinician must consider a biopsy if there are signs and symptoms that suggest a serious underlying etiology such as leukemia or tuberculosis. The typical features of drug-influenced gingival overgrowth include an increase in collagen fibers, inflammatory infiltration, acanthosis and elongated rete pegs.14,15

The prevalence of gingival enlargement in healthy populations has been estimated to be between 4.0 and 7.5 percent.10,12 Prevalence has been known to vary from 10 to 50 percent in populations of patients receiving phenytoin therapy.7,11,16,17 Although the pharmaceutical effect and primary target tissues of antiepileptic, immunosuppressant, antidepressant and calcium channel blocker medications are different, they act similarly on gingival connective tissue, causing fibrous gingival enlargement.18 In cases involving gingival enlargement, gingival connective tissue does not necessarily exhibit an increased number of fibroblasts histologically.6,19 These findings indicate that, at a molecular level, one etiologic factor of drug-induced gingival enlargement may be the inhibition of collagen phagocytosis by means of reducing the expression of $\alpha_\beta_1$ integrins.6 Research suggests that integrins transduce information from the extracellular matrix to the inside of the cell by triggering intracellular signaling pathways.6 Antiepileptic, immunosuppressant, antidepressant and calcium channel blocker drugs are known to act as calcium antagonists. Intracellular calcium plays a role in the regulation of $\alpha_\beta_1$ integrin-mediated collagen phagocytosis by altering integrin affinity. Furthermore, the actin-binding protein gelsolin is considered an important factor in gingival enlargement. Gelsolin contributes to the maintenance of normal tissue integrity by regulating collagen phagocytosis through its integrin-binding affinity to collagens.6

**Treatment.** Risk factors associated with phenytoin-induced gingival enlargement may have a synergistic effect, and bacterial plaque appears to be the most important determinant of severe phenytoin-influenced gingival enlargement.9 Still, to date, the most effective long-term treatment for gingival enlargement is drug withdrawal.5 In addition to discontinuation of drug treatment, periodontal therapy often is recommended in conjunction with oral hygiene instructions. Dannewitz and colleagues20 showed that in patients who were receiving calcium channel blockers, nonsurgical therapy for gingival enlargement consisting of full-mouth gross debridement, scaling and root planing and short-term (two weeks’) use of 0.12 percent chlorhexidine gluconate mouthrinse resulted in only 6 percent of teeth’s requiring surgical intervention.

**DIFFERENTIAL DIAGNOSIS**

**Hereditary gingival enlargement.** Patients with hereditary gingival enlargement exhibit clinical signs identical to those of the patient described here. This diagnosis can be excluded by questioning the patient about whether his or her family members have similar gingival enlargement. As an isolated abnormality, gingival enlargement is inherited as an autosomal dominant trait or, rarely, as an autosomal recessive trait.21,22 Gingival enlargement may arise owing to a spontaneous gene mutation, so a neg-
ative family history alone cannot dismiss hereditary gingival enlargement from the differential diagnosis completely. Gingival enlargement has been associated rarely with a number of syndromes such as inclusion-cell disease (mucolipidosis II), acanthosis nigricans, Borronne di Rocco Crovato syndrome, Cantu syndrome and Winchester syndrome. In this patient, there were no systemic signs of a syndromic presentation. However, as this patient did not have any siblings and we do not know whether the gingival enlargement predated her receipt of antiseizure medications, the isolated genetic form of the gingival enlargement cannot be ruled out definitively.

**Leukemic infiltration.** Leukemic infiltration can be varied in appearance, but it almost always involves gingival enlargement. The tissue often is purple-red, a condition that also can be seen in other forms of gingival enlargement with secondary inflammation. Leukemic infiltration usually features an acute onset of hemorrhagic gingival oozing. Considering that the duration of the patient’s gingival enlargement was at least eight months, it is likely that she would have exhibited other signs and symptoms of leukemia such as bleeding tendencies, lymphadenopathy, recurrent infections, weight loss, lethargy or a combination of these.

**Tuberculosis.** Tuberculosis and other granulomatous diseases—including orofacial granulomatosis, Crohn disease and sarcoidosis—can mimic drug-induced gingival enlargement clinically. In the case of the patient we describe, the generalized nature of the gingival enlargement suggests that it was not tuberculosis or another granulomatous disease. Also, the results of the histologic examination did not show granuloma formation or an inflammatory process but were consistent with drug-induced gingival enlargement.

**CONCLUSION**

Gingival enlargement is not always associated with a patient’s medication regimen. The differential diagnosis for a patient with gingival enlargement should include hereditary influences, leukemic infiltration and granulomatous diseases such as tuberculosis. The clinician should obtain an in-depth medical history to investigate a diagnosis of hereditary gingival enlargement, although there is always the possibility that the gingival changes can arise because of a spontaneous gene mutation. If there are signs and symptoms suggesting a systemic disease such as leukemia or tuberculosis, appropriate diagnostic testing such as blood testing or biopsy must be considered. Patients with gingival enlargement should undergo appropriate laboratory testing to ensure that any underlying disorders are diagnosed and treated at the earliest possible time.

When this article was written, Dr. Pette was a second-year resident in the postgraduate program in periodontology, Department of Periodontology, College of Dental Medicine, Nova Southeastern University, Fort Lauderdale-Davie, Fla. He now is in private practice in Fort Myers, Fla.

Dr. Siegel is a professor and the chair, Department of Diagnostic Sciences, College of Dental Medicine, Nova Southeastern University, 3200 S. University Drive, Fort Lauderdale-Davie, Fla. 33328-2018, e-mail “masiegel@nova.edu”. He also is a coeditor of the Diagnostic Challenge section. Address reprint requests to Dr. Siegel.

Dr. Parker is an associate professor and the chair, Department of Periodontology, College of Dental Medicine, Nova Southeastern University, Fort Lauderdale-Davie, Fla.

**Disclosure.** None of the authors reported any disclosures.

Diagnostic Challenge is published in collaboration with the American Academy of Oral and Maxillofacial Pathology and the American Academy of Oral Medicine.