Drug-Induced Gingival Hyperplasia

- Author: Lina M Mejia, DDS; Chief Editor: William D James, MD more...

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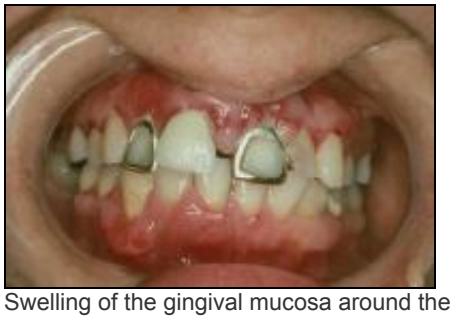
Background

Several causes of gingival hyperplasia are known, and the most recognized is drug-induced gingival enlargement. Furthermore, causes of congenital gingival enlargement include hereditary and metabolic disorders, such the fetal valproate syndrome.[1]



Swelling of the gingival mucosa around the right lower canine and multiple areas of erythema, erosions, and bleeding throughout the upper gingival mucosa.

Gingival overgrowth, also known as gingival hyperplasia secondary to drugs, was first reported in the dental literature in the early 1960s in institutionalized epileptic children who were receiving therapy with phenytoin (Dilantin) for the treatment of seizures. Cyclosporine, a potent immunosuppressant widely used since the early 1980s in organ transplant recipients and for psoriasis, and numerous calcium channel blocker agents, including nifedipine and amlodipine, have also been associated with gingival overgrowth.[2] Nifedipine appears to have an additive effect when used together with cyclosporine in transplant recipients with hypertension. In addition, phenobarbital-induced gingival overgrowth has been reported but is rare and needs further evaluation.[3]

Because not all patients on phenytoin, cyclosporine, and/or calcium antagonists develop gingival overgrowth, identifying patients at risk is important in order to take all the necessary measures to minimize the onset and severity of this condition.

Currently, the etiology of drug-induced gingival overgrowth is not entirely understood but is clearly multifactorial. Debate is ongoing regarding whether drug-induced gingival overgrowth is due to hyperplasia of the gingival epithelium or of submucosal connective tissue, and/or both. Furthermore, the effect of age, sex, and duration and dosage of the drug in the pathogenesis of gingival overgrowth is not clearly understood. One of the main reasons is that clinical and epidemiologic studies are primarily retrospective, and they are unable to fully clarify this association.

Some of the risk factors known to contribute to gingival overgrowth include the presence of gingival inflammation (ie, gingivitis) resulting from poor oral hygiene. Furthermore, the presence of dental plaque may provide a reservoir for the accumulation of phenytoin or cyclosporine. In orthodontic patients, gingival overgrowth has been suggested to be due to nickel accumulation and epithelial cell proliferation.[4]

Other intrinsic risk factors include the susceptibility of some subpopulations of fibroblasts and keratinocytes to phenytoin, cyclosporine, and/or nifedipine, and the number of Langerhans cells present in oral epithelium.[5, 6] The latter appears to be related to the presence of inflammation and dental plaque.

Because most of the studies reported to date observed patients who had gingival overgrowth at the time of the study, determining the true effect of the medication independent of cofactors such as severity of the underlying disease, oral health status prior to the onset of gingival overgrowth (eg, premature tooth loss, periodontal disease, routine oral hygiene), socioeconomic status, and education is quite difficult. However, the status of oral health prior to onset of GO combined with the medication are both clearly involved in the onset of drug-induced gingival hyperplasia.[7]

Pathophysiology

Several studies have shown that the interaction of phenytoin, cyclosporine, and nifedipine with epithelial keratinocytes, fibroblasts, and collagen can lead to an overgrowth of gingival tissue in susceptible individuals. Phenytoin has been shown to induce gingival overgrowth by its interaction with a subpopulation of sensitive fibroblasts. Cyclosporine has been suggested to affect the metabolic function of fibroblast (eg, collagen synthesis, breakdown), whereas nifedipine, which potentiates the effect of cyclosporine, reduces protein synthesis of fibroblasts. A review of existing literature shows that a cofactor clearly is needed to induce gingival overgrowth.[5, 8, 9, 10, 11, 12, 13] In fact, several lines of evidence point to a modulation of inflammatory processes.

Epidemiology

Frequency

United States

Gingival overgrowth is a rare condition, and no population-based or epidemiologic studies exist in the United States. Incidence rates are reported from case-series studies. The prevalence of phenytoin-induced gingival overgrowth is estimated at 15-50% in patients taking the medication. The prevalence for cyclosporine transplant recipient patients is 27%; however, these numbers should be interpreted with caution. The incidence of gingival hyperplasia has been reported as 10-20% in patients treated with calcium antagonists in the general population. Clinicians should look at the population represented within each particular study (ie, young persons with epilepsy, recipients of transplants).

International

No incidence or prevalence epidemiologic data is available on gingival overgrowth worldwide. In India, 57% of epileptic children aged 8-13 years who were undergoing phenytoin monotherapy developed gingival overgrowth within 6 months of treatment.

Mortality/Morbidity

No mortality is associated with gingival enlargement. Morbidity can be severe in some cases because of gross overgrowth of gingival tissue, which can lead to gingival bleeding, pain, teeth displacement, and periodontal disease.

Race

No racial predilection exists for the onset of drug-induced gingival overgrowth.

Sex

No sexual predilection exists for drug-induced gingival overgrowth, although in one study, males were 3 times

more likely than females to develop gingival overgrowth with calcium antagonists.

Age

No age predilection exists for the onset of drug-induced gingival overgrowth; however, phenytoin-induced gingival overgrowth appears to be more frequent in young patients with epilepsy. Most likely, this may be related to the age of the population, the nature of the disease, and poor oral hygiene.

Contributor Information and Disclosures

Author
Lina M Mejia, DDS Assistant Professor, Oral Medicine and Diagnostic Sciences, College of Dental Medicine, Nova Southeastern University

Lina M Mejia, DDS is a member of the following medical societies: American Academy of Oral Medicine, American Dental Association, and California Dental Association

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Coauthor(s)
Francina Lozada-Nur, DDS, MS, MPH Professor Clinical Oral Medicine (Emerita), University of California at San Francisco School of Dentistry

Francina Lozada-Nur, DDS, MS, MPH is a member of the following medical societies: American Academy of Oral Medicine

Disclosure: Nothing to disclose.

Specialty Editor Board
Franklin Flowers, MD Chief, Division of Dermatology, Professor, Department of Medicine and Otolaryngology, Affiliate Associate Professor of Pediatrics and Pathology, University of Florida College of Medicine

Franklin Flowers, MD, is a member of the following medical societies: American College of Mohs Micrographic Surgery and Cutaneous Oncology

Disclosure: Nothing to disclose.

David F Butler, MD Professor of Dermatology, Texas A&M University College of Medicine; Chair, Department of Dermatology, Director, Dermatology Residency Training Program, Scott and White Clinic, Northside Clinic

David F Butler, MD is a member of the following medical societies: Alpha Omega Alpha, American Academy of Dermatology, American Medical Association, American Society for Dermatologic Surgery, American Society for MOHS Surgery, Association of Military Dermatologists, and Phi Beta Kappa

Disclosure: Nothing to disclose.

Drore Eisen, MD, DDS Consulting Staff, Department of Dermatology, Dermatology Research Associates of Cincinnati

Drore Eisen, MD, DDS is a member of the following medical societies: American Academy of Dermatology, American Academy of Oral Medicine, and American Dental Association

Disclosure: Nothing to disclose.

Glen H Crawford, MD Assistant Clinical Professor, Department of Dermatology, University of Pennsylvania School of Medicine; Chief, Division of Dermatology, The Pennsylvania Hospital

Glen H Crawford, MD is a member of the following medical societies: Alpha Omega Alpha, American Academy of Dermatology, American Medical Association, Phi Beta Kappa, and Society of USAF Flight Surgeons

Disclosure: Nothing to disclose.

Chief Editor
William D James, MD Paul R Gross Professor of Dermatology, Vice-Chairman, Residency Program Director, Department of Dermatology, University of Pennsylvania School of Medicine

William D James, MD is a member of the following medical societies: American Academy of Dermatology and Society for Investigative Dermatology

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Additional Contributors
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