Histo-Pathological Evaluation of Drug Allergy Observed With Gingival Overgrowth Induced by Phenytoin: A Case Report*

SUMMARY
Gingival overgrowths are lesions which can be seen due to different reasons. Phenytoin (PHT), the drug used in the treatment of epilepsy, is probably one of the commonest causes of gingival overgrowth. In the presented case, a male patient aged 23, who has been taking PHT for the treatment of epilepsy, subsequently manifested by the enlarged gingival tissue, which was cut out using gingivectomy procedure. The biopsy samples, which were taken during surgery, were assessed histopathologically. Histopathological evaluation showed that there were deepened rete-peg structures, and a connective tissue rich in collagen substance. Moreover, a dense plasmocyte cell infiltration was observed. This fact was interpreted as an allergic effect in gingival tissue caused by PHT.

Keywords: Overgrowth, gingival; Phenytoin; Drug Allergy

Introduction
Gingival enlargement or overgrowth has been associated with multiple factors including inflammation, side effects of drugs, and neoplastic conditions. Chronic inflammation due to accumulation of dental plaque frequently causes gingival overgrowth1. Drugs associated with gingival enlargement include anti-epileptics, like phenytoin2-5, cyclosporin6,7, and calcium antagonists, such as dihydropyridines8,9, verapamil10,11, and diltiazem. The clinical and pathologic features in drug-induced gingival overgrowth are independent of the drug administered, which suggests a common pathway of induction12. The pathogenic mechanisms of gingival enlargement involve different factors, such as dental plaque, presence of genetically predetermined gingival fibroblasts (named responders), and effect of the drug itself, with all compounds affecting the trans-membrane flow of calcium13,14. This in turn changes the metabolism of connective tissue fibroblasts, causing an increase in the components of the extra-cellular matrix, i.e. collagen fibres and/or ground substance15,16.

Epilepsy is a condition in which a person has recurrent seizures due to a chronic underlying process. A seizure is a paroxysmal event, due to abnormal central nervous system activity, that can have various manifestations ranging from dramatic convulsive activity, with or without loss of consciousness, to phenomena not discernible by an observer17. Currently available anti-epileptic drugs act by depressing the neuronal activity in the focus of origin or by blocking the spreading mechanisms.

Phenytoin (PHT, 5,5-diphenylhydantoin) was first introduced as an anti-epileptic drug, in 193818. It is slowly absorbed from the gastrointestinal tract, and shows marked inter individual variation19. PHT is known to concentrate in the brain, at levels 5 to 10 times that found in the serum20. The drug is extensively metabolized in the liver by microsomal enzymes, with the major metabolite (50-5% of the PHT dose) being 5-(p-hydroxyphenyl)-5-phenylhydantoin (p-HPPH)21. The drug has been proposed to act via stabilization of the neuronal cell membranes and through suppression of synaptic transmissions. Depending on the membrane conditions, drug concentration and timing, it appears that PHT acts by affecting the (Na+ K) pump, Ca++ transport, or the sodium influx at a cellular level22.
Gingival overgrowth is one of the most common side effects associated with the administration of PHT, the most frequently used anti-epileptic drug. Gingival overgrowth, in relation to PHT, was first described in 1939, with several other subsequent authors reporting the overgrowth associated with phenobarbital, valproic acid and vigabatrin. Gingival overgrowth has not been associated with carbamazepine, a useful alternative medication in the treatment of patients with seizures that have, or are at risk of, gingival enlargement.  

Case Report

A male patient aged 23 with gingival enlargements was referred to the Department of Periodontology, Faculty of Dentistry at the University of Cumhuriyet. In the first step, his dental and medical history was taken and he was clinically examined. The patient had not received any prior dental therapy. In his medical history, it was determined that he has been taking medicaments (Phenytoin sodium 100mg; 2x2, and Barbexaclone 100 mg; 2x1) for the treatment of epilepsy for 3 years, which was diagnosed in the department of neurology. There were severe gingival overgrowths in all quadrants and in both buccal and oral sides of the mouth (Fig. 1). A mild inflammation and bleeding on probing were also recorded. It was thought the gingival overgrowth was due to PHT usage. However, it was not possible to stop or decrease the drug dosage for our patient.

A radiographic examination revealed no supporting bone loss except the area of the tooth 46; however, teeth 11, 17, 21, 26, 27, 35, 36, 37, 46, and 47 were carious (Fig. 2). First molar on the right lower jaw (46) was extracted due to a serious caries, and teeth 11, 12, 13, 21, 22, 23 were treated aesthetically; the conservative and endodontic treatment of other teeth is continuing. After medical history and clinical examination, a treatment phase I (periodontal treatment) was performed. 3 weeks after the treatment phase I, periodontal tissues were evaluated again and it was decided to perform a gingivectomy operation and remove gingival enlargements. The biopsy samples were taken during the operation and were subsequently assessed histo-pathologically. Histo-pathological evaluation showed that there were deepened rete-peg structures, thickened epithelial zone and a connective tissue rich in collagen substance. Moreover, a striking plasmocyte cell infiltration was observed (Fig. 3).

Oral hygiene applications were instituted at each appointment due to achieve an adequate plaque control; and it was achieved. The patient is still being followed-up, and is under control (Fig. 4).
Discussion

A gingival overgrowth is a common feature of gingival disease. There are many types of gingival overgrowth, varying in accordance to etiological factors and pathological processes producing them. Gingival overgrowth caused by PHT, usually begins as a painless, bead-like, and diffuse swelling of the interdental papillae, which enlarge and coalesce, leaving a nodular appearance. As the condition progresses, the marginal and papillary overgrowths unite; they may develop into a massive tissue fold covering a considerable portion of the crowns. The overgrowth is chronic, and slowly increases in size, recurs when surgically removed, and has been reported to disappear spontaneously soon after the discontinuation of the drug. A PHT-induced gingival overgrowth begins as hyperplasia of the connective tissue core of the marginal gingiva, followed by proliferation of the epithelium. The overgrowth increases by proliferation and expansion of the central core beyond the crest of the gingival margin.

There are various risk factors that have been elucidated for a drug-induced gingival overgrowth. The identifiable factors can be considered under the following headings: age, oral hygiene, daily dose and duration of drug therapy. The role of oral hygiene in the pathogenesis of gingival overgrowth is also complex. The presence of the overgrowth makes plaque control difficult by helping the plaque retention, resulting in a secondary inflammatory process, complicating the gingival hyperplasia caused by the drug. Effective plaque control may reduce and prevent gingival enlargement. In addition to plaque control and medical management, periodontal surgical treatment and multidisciplinary dental care are a key strategy in managing gingival enlargement.

Mild gingival enlargement may only require local management, as improvement in oral hygiene together with professional cleaning of the teeth, which can lead to resolution of inflammation and reduction in gingival enlargement. But, if there is a serious gingival overgrowth like in our case, a periodontal surgical management is required to remove the excess tissue. In our case, gingiva had almost covered the full portion of the crowns in all quadrants. It was very difficult to achieve an adequate oral hygiene for the patient. And there was a serious aesthetical problem which affected psychological condition of the patient. In cases that have gingival enlargement covering more than about a third of the tooth surface, a consideration should be given to altering the medication. When possible, reducing the dose or changing to another drug may bring about partial or complete regression of the lesion. But this was not possible for our patient, so we warned our patient about the possibility of gingival enlargement recurring despite periodontal treatment.

The relationship between anticonvulsant drugs and hypersensitivity has been shown in the literature. In our case; the histo-pathological evaluation of the specimens has revealed deepened rete-peg structures and a connective tissue rich in collagen substance. These findings are classical for some gingival overgrowths, but a dense plasmocyte cell infiltration was also observed. We are of the opinion that this finding could be a result of an allergic background caused by PHT.

As a conclusion, in gingival enlargement cases, plaque control is very important. Treatment required in accordance to the degree of gingival enlargement must be performed and the importance of maintaining good oral hygiene, as a preventive measure, should be emphasized. In addition, the possible allergic drug effects should be known and if possible, the alternative medications may be considered. If there is not a chance of changing the medication, the possibility of recurrence should be told to the patient.

References


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