CASE REPORT

Phenytoin-induced severe gingival overgrowth in a child

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SUMMARY

Gingival enlargement or overgrowth (GO) is a common complication of the anticonvulsant drug phenytoin (PHT). GO is evident in almost half of the patients receiving PHT therapy. PHT-induced gingival overgrowth (PGO) is more common in children than in adults and affects both males and females equally. PGO may vary from mild to severe and does not seem to be dose dependant. It is supposed that PHT and its metabolites cause a direct effect on the periodontal tissues; however, poor oral hygiene may contribute to the severity of gingival inflammation in patients with PGO. Management of PGO includes meticulous oral hygiene practice to reduce inflammation and surgical excision of the overgrown tissue, known as gingivectomy. We present a case of PHT-induced severe GO in a 10-year-old boy and discuss the clinical features, aetiology, pathogenesis and management of PGO.

BACKGROUND

Among the various causes of gingival overgrowth (GO), drug-induced GO may be caused by three different classes of drugs—antiepileptics, calcium channel blockers and immunosuppressant. The most common drug associated with GO is the anti-epileptic drug phenytoin (PHT). However, other antiepileptic drugs such as phenobarbital and valproate may also cause GO in rare cases. PGO usually starts 3 months after taking the drug¹ and develops most rapidly in the first year.² Children are more frequently affected than adults³ with equal distribution in both the genders.⁴

The exact aetiological factors responsible for the development of PGO are still unclear; however, some contributory factors have been found associated with PGO. These include bacterial biofilm, inflammation, genetic factors and other risk factors.⁵ 'Drug-induced gingival diseases' were categorised as 'dental plaque-induced gingival diseases' in the most recent classification system for periodontal diseases.⁶ In this classification, dental plaque is considered as a major contributory factor in the aetiology of drug-induced GO. The role of chronic inflammation as a contributory factor in the development of PGO can be described by the fact that chronic inflammation resulting from persistent irritating agent usually leads to fibrosis as a part of reparative process. The affected gingival tissue in patients with PGO has less inflammation and more fibrosis.⁷ Genetic factors may also play a significant role in the development of PGO as not all patients receiving PHT therapy develop GO. Genetic factors could affect a patient's susceptibility

to the unwanted effects of PHT by influencing several factors involved in drug-plaque-induced inflammation.⁵

Clinically PGO starts as a diffuse swelling of the free gingival and interdental papillae of the maxillary and mandibular anterior teeth which may later coalesce to form nodules.⁸ In severe cases, most of the clinical crowns of the maxillary and mandibular teeth are covered. The treatment of severe PGO includes meticulous plaque control measures and surgical removal of the enlarged tissue. We present a case of PGO in a 10-year-old boy.

CASE PRESENTATION

A 10-year-old boy reported to the department of paediatric and preventive dentistry with painless gingival swelling and difficulty in eating. The gingival swelling was present since the past 2.5 years. A careful medical history of the patient was recorded, which revealed previous episodes of epileptic convulsions since the past 3 years; however, history of any other systemic disease was negative. On general examination, the patient was healthy with normal gait and gesture. Extraoral examination of the patient showed protuberant gingival nodules in between the lips (figure 1). The patient was not able to close his lips because of the gingival nodules. On intraoral examination, the patient had profuse GO (figure 2) that was non-tender and did not bleed on probing. Clinically the swelling appeared non-inflammatory and fibrous.

The patient was under medication for epileptic convulsions since the past 3 years. The patient was prescribed PHT, phenobarbital and cefoxitin by his physician and was taking these medicines regularly since the past 3 years. Orthopantomogram radiograph of the patient revealed interdental bone loss in the maxillary and mandibular anterior teeth (figure 3). Since the clinical features were consistent with PGO, surgical excision of the enlarged gingival tissue was planned, as surgical excision is the only available treatment in such cases of severe PGO. Before surgical excision, thorough oral prophylaxis of the patient was performed. Surgical excision was performed under local anaesthesia in two visits; in the first visit, tissue was excised from mandibular arch while in the second visit from maxillary arch. The gingivectomy and gingivoplasty procedures were performed with the help of scalpel no. 12 and 15, periodontal knives (Kirkland and Urban's knives) and curettes, as described by Camargo *et al.*⁹ Following surgical excision, a surgical dressing and periodontal pack (Coe-Pak

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Figure 1 Extraoral photograph showing protuberant gingival swelling.

Automix) was placed. The excised tissue was sent for histopathological and immunohistochemical examination.

INVESTIGATIONS

Histopathological examination revealed the presence of stratified squamous epithelium with pseudo infiltrate nets of squamous epithelium extending into the underlying subepithelium. It also showed the elongation and thickening of rete pegs and cytological atypia. The underlying subepithelial tissue also showed chronic inflammatory cell infiltrate (figures 4 and 5).

On immunohistochemical examination, Ki-67 was expressed in the basal one-third of the epithelial cells. However, maturing squamous cells did not show Ki-67 expression (figure 6). These findings were consistent with pseudoepitheliomatous hyperplasia. Ki-67 examination was carried out because Ki-67 is a proliferation associated antigen that is useful for objective histopathological evaluation of tumour proliferation activity.

OUTCOME AND FOLLOW-UP

The patient was recalled after 7 days to remove Coe-Pak dressing. The healing was uneventful (figure 7). The patient's physician was requested to replace PHT with alternative drugs. The

Figure 2 Intraoral view showing nodular appearance of the swelling.

Figure 3 Orthopantomogram radiograph revealing interdental bone loss in the maxillary and mandibular anterior teeth.

postoperative follow-up was continued up to 18 months. During that period, the gingival overgrowth did not recur.

DISCUSSION

PHT, an anticonvulsant drug, is used along with phenobarbital or other anticonvulsants, to prevent or treat generalised tonic-clonic seizures, complex partial seizures or seizures occurring during or after neurosurgery. One of the major side effects of antiepileptic drugs, particularly PHT, is GO. PHT in most of the times (approximately 50%) associated with GO; however, in few instances, phenobarbital and rarely valproic acid may also cause GO.

Dummett¹⁰ suggested that after taking PHT, GO becomes apparent in the first 3 months while Aas¹¹ suggested that the overgrowth is more rapid in the first year. The patient was on PHT therapy for the past 3 years and developed GO 2.5 years ago, that is, 6 months after taking the medicine. The PGO increased consistently since then and it covered the clinical crowns of the maxillary anterior teeth completely and almost half of the clinical crowns of the mandibular anterior teeth. The patient was suggested to visit a dental surgeon by his neurologist but he was not very much concerned about the growth until he experienced difficulty in eating.

Clinically, the GO starts as a diffuse swelling in the labial and lingual interdental papillae of the maxillary and mandibular anterior teeth which may later coalesce to form nodules. The clinical crowns of the maxillary and mandibular teeth may be completely covered in severe PGO. Gingival enlargement is

Figure 4 Microphotograph showing pseudo-infiltrate nets of squamous epithelium extending into the underlying subepithelium.

Figure 5 Microphotograph showing elongation and thickening of rete pegs, cytological atypia and chronic inflammatory cell infiltrate.

greatest in the labial aspect of the maxillary and mandibular anterior teeth. The severity of PGO does not seem to be dose dependent. The colour of the overgrowth depends on the amount of inflammatory infiltrate present in the tissue and may range from coral pink to a deep bluish red.¹² In the present case, the tissue had a nodular appearance; maxillary nodules were very large and the colour of the gingival tissue was coral pink. The clinical crowns of the maxillary anterior teeth were completely covered and almost half of the clinical crowns of the mandibular anterior teeth were covered with enlarged gingival tissue which was most severe in the labial aspect of maxillary anterior teeth.

The exact aetiology of GO in patients on PHT therapy is still unknown. Genetic factors may be contributing to PGO as not

Figure 6 Immunohistochemical examination showing Ki-67 expression in basal one-third of the epithelial cells.

Figure 7 One-week postoperative clinical photograph.

all patients on PHT therapy develop GO. It was suggested that approximately 50% of patients on PHT develop GO. Evidence suggests that certain factors which play an important role in the drug-plaque-induced inflammation like drug metabolism, collagen synthesis, collagenolytic activity and gingival fibroblast functional heterogeneity could be influenced by a patient's genetic susceptibility to unwanted effects of PHT therapy.^{5 13 14} Poor oral hygiene may be a contributory factor as the bacteria present in plaque may cause inflammation of the gingival lesions.¹⁵ The patient was not able to brush his teeth properly because of the severity of the GO. The most recent classification system for periodontal disease includes 'dental plaque-induced gingival diseases' as a major group of the category 'drug-induced gingival diseases'.⁶ However, controversial studies exist in the literature regarding the possible role of dental plaque/certain species of bacteria in the development or advancement of drug induced GO. The prevalence of certain bacterial species like *Prevotella intermedia*, *Treponima denticola* and *Porphyromonas gingivalis* was found to be higher in patients with PGO in some studies.^{16 17} However in other studies, no difference in the bacterial population was found in patients on PHT therapy with and without GO.^{18 19} Controversies also exist whether maintenance of good oral hygiene can prevent or reverse GO. Chronic inflammation is also considered as one of the contributory factors in the development of PGO. Chronic inflammation caused by a persistent irritating agent usually results in tissue fibrosis as a part of reparative process. Inflammatory cells such as macrophages and lymphocytes produce cytokine and chemokines which regulate gingival tissue repair and remodelling.²⁰ Suzuki *et al* suggested that PHT may regulate the expression of cytokines in gingival tissues.²¹

The exact pathogenesis of PGO remains unclear; however, it is suggested that PHT and its metabolites exert a direct effect on gingival tissues.^{2 22} Other less accepted hypotheses include immunosuppression of long-term PHT, alteration in the metabolism of adrenal glands leading to adrenal-cortical unresponsiveness, stimulation of sodium pump acting as a stimulus of fibroblasts and folic acid depletion, increased sulfated glycosaminoglycans, gingival phenotype population differences, reduced collagen activity and disruption of fibroblast cellular $\text{Na}^+/\text{Ca}^{++}$ flux.

Management of GO includes meticulous plaque control to reduce inflammation and surgical removal of the enlarged tissue. The surgery has to be repeated at frequent intervals as the overgrowth has an insidious progressive nature.²³ The present patient underwent surgical management of the GO; a

procedure known as gingivectomy, which is the only available treatment option in cases of drug induced GO.

Since PHT is the most commonly used antiepileptic drug and its adjustment to establish a level of seizure control without sacrificing alertness and mood control is a long and tedious process, neurologists and patients are sometimes reluctant to change an ongoing anticonvulsant programme.²⁴ However from a dental surgeon's point of view, it is suggested that a neurologist should consider an alternative drug for PHT since GO is a very common complication of PHT therapy and quality of life of concerned children is severely affected by the GO not only because of eating problems but also due to aesthetic reasons.

Learning points

- Gingival overgrowth is a common side effect of the most commonly used antiepileptic drug phenytoin.
- In severe cases of GO, surgical management is the only available treatment option which may have to be repeated because of the insidious nature of the disease.
- An alternative drug to phenytoin should be considered by the neurologists, wherever possible.

Competing interests None.

Patient consent Obtained.

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REFERENCES

- 1 Hassell T, O'Donnell J, Pearlman J, et al. Phenytoin induced gingival overgrowth in institutionalized epileptics. *J Clin Periodontol* 1984;11:242–53.
- 2 Hassell TM. Epilepsy and the oral manifestations of phenytoin therapy. *Monogr Oral Sci* 1981;9:1–205.
- 3 Klar LA. Gingival hyperplasia during dilantin therapy; a survey of 312 patients. *J Public Health Dent* 1973;33:180–5.
- 4 Sanders BJ, Weddell JA, Dodge NN. Managing patients who have seizure disorders: dental and medical issues. *J Am Dent Assoc* 1995;126:1641–7.
- 5 Corrêa JD, Queiroz-Junior CM, Costa JE, et al. Phenytoin-induced gingival overgrowth: a review of the molecular, immune, and inflammatory features. *ISRN Dent* 2011;2011:497850.
- 6 Dongari-Baqtzoglou A. Research, Science and therapy committee, american academy of periodontology. Drug-associated gingival enlargement. *J Periodontol* 2004;75:1424–31.
- 7 Trackman PC, Kantarci A. Connective tissue metabolism and gingival overgrowth. *Crit Rev Oral Biol Med* 2004;153:165–75.
- 8 Angelopoulos AP. Diphenylhydantoin gingival hyperplasia. A clinicopathological review 1. Incidence, clinical features and histopathology. *Dent J* 1975;41:103–6.
- 9 Camargo PM, Carranza FA, Takei HH. Treatment of gingival enlargement. In: Newman MG, Takei HH, Klokkevold PR, Carranza FA, et al. eds. *Carranza's clinical periodontology for South Asia*. 11th edn. India: Elsevier, 2012:556–61.
- 10 Dummett CO. Oral tissue reactions from dilantin medication in the control of epileptic seizures. *J Periodontol* 1954;25:112–22.
- 11 Aas E. Hyperplasia gingivae diphenylhydantoinea. A clinical, histological, and biochemical study. *Acta Odontol Scand* 1963;21:1–142.
- 12 Esterberg HL, White PH. Sodium dilantin gingival hyperplasia. *J Am Dent Assoc* 1945;32:16–24.
- 13 Hassell TM, Hefti AF. Drug-induced gingival overgrowth: old problem, new problem. *Crit Rev Oral Biol Med* 1991;2:103–37.
- 14 Hassell TM, Page RC, Narayanan AS, et al. Diphenylhydantoin [Dilantin] gingival hyperplasia: drug-induced abnormality of connective tissue. *Proc Natl Acad Sci USA* 1976;73:2909–12.
- 15 Mariotti A. Dental plaque-induced gingival diseases. *Ann Periodontol* 1999;4:7–19.
- 16 Takada K, Sugiyama H, Umezawa K, et al. The subgingival microflora in phenytoin-induced gingival hyperplasia. *J Periodontol Res* 2003;38:477–81.
- 17 Miyazaki H. Association between phenytoin-induced gingival hyperplasia and periodontopathic bacteria in institutionalized patients with severe motor and intellectual disabilities. *Kokubyo Gakkai Zasshi* 2010;77:140–8.
- 18 Yamada H, Nishimura F, Furuno K, et al. Serum phenytoin concentration and IgG antibody titre to periodontal bacteria in patients with phenytoin-induced gingival overgrowth. *J Int Acad Periodontol* 2001;3:42–7.
- 19 Smith QT, Wilson MM, Germaine GR, et al. Microbial flora and clinical parameters in phenytoin associated gingival overgrowth. *J Periodontol Res* 1983;18:56–66.
- 20 Trackman PC, Kantarci A. Connective tissue metabolism and gingival overgrowth. *Crit Rev Oral Biol Med* 2004;15:165–75.
- 21 Suzuki AM, Yoshimura A, Ozaki Y, et al. Cyclosporin A and phenytoin modulate inflammatory responses. *J Dent Res* 2009;88:1131–6.
- 22 Conard GJ, Haavik CO, Finger KF. The relationship of 5,5-diphenylhydantoin metabolism to the species-specific induction of gingival hyperplasia in the rat. *Arch Oral Biol* 1972;17:311–21.
- 23 Glickman I. Hyperplasia of the gingiva associated with dilantin therapy. *J Am Dent Assoc* 1941;28:199–207.
- 24 Reynolds NC Jr, Kirkham DB. Therapeutic alternatives in phenytoin-induced gingival hyperplasia. A case report and discussion. *J Periodontol* 1980;51:516–20.

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