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◆증 례

Valproate 연관 치은 증식 : 증례 보고

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Abstract

VALPROATE-INDUCED GINGIVAL OVERGROWTH : A CASE REPORT

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Drug-induced gingival overgrowth is an abnormal increase of gingival tissues caused as a side effect of systemic medication.

This report presents a severe case of valproate-induced gingival overgrowth combined with ulcerative and hemorrhagic lesions in a patient with Lennox-Gastaut syndrome. Considering the patient's limited cooperative ability, gingivectomy and excisional biopsy under general anesthesia were performed. The lesions were successfully treated without recurrence.

When gingival enlargement does not subside with nonsurgical treatments, surgical procedure and excisional biopsy are to be performed. Postoperative management of oral hygiene is critical to prevent recurrence. **[J Korean Dis Oral Health Vol.14, No.2: 92-96, December 2018]**

Key words : Drug-induced gingival overgrowth, Valproate, Lennox-Gastaut syndrome, Gingivectomy

Ⅰ. Introduction

Gingival overgrowth, also known as gingival enlargement or gingival hyperplasia, is an abnormal increase of gingival tissues. Gingival overgrowth can be caused by several factors; (1) inflammatory gingival enlargement, (2) medication-induced gingival enlargement, (3) hereditary gingival fibromatosis, and (4) systemic causes of gingival enlargement[1]. The treatment depends on the underlying cause.

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Drug-induced gingival overgrowth occurs in whole or in part from systemic medication. It occurs as a side effect following systemic drug use for non-dental treatments: phenytoin, an antiepileptic; cyclosporine A, an immunosuppressant; and calcium channel blockers such as nifedipine, verapamil, and amlodipine for cardiovascular diseases. These drugs cause critical changes in fibroblast function, which result in an increase in the extracellular matrix of the gingival connective tissue[2].

Drug-induced gingival overgrowth generally initiates on interdental gingival papillae in anterior teeth, usually within two or three months after initiation of medication. The severity of gingival enlargement may be related to the dose, duration, and plasma levels of the drug, but some studies argue against this concept. Many studies have reported a significant correlation

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between the level of plaque and calculus accumulation and the severity of gingival overgrowth[3,4].

Although the side effect of phenytoin on gingival overgrowth is widely known, other anticonvulsant drugs such as barbiturate, valproic acid, succinimides, and carbamazepine have been rarely reported to induce gingival overgrowth[3-5]. The incidence of gingival overgrowth caused by these drugs is low compared to that of phenytoin-induced gingival overgrowth.

This report presents a severe case of valproate-induced gingival overgrowth combined with ulcerative and hemorrhagic lesions that occurred in all four quadrants in a patient with Lennox-Gastaut syndrome.

Ⅱ. Case Report

A 7-year-3-month-old male patient visited Department of Pediatric Dentistry, Yonsei University Dental Hospital with the chief complaint of enlargement of gingiva and bleeding. The patient was known to have had Lennox-Gastaut syndrome and was on medication since last seven years; valproic acid, rufinamide, levetiracetam, and phenobarbital. He had severe mental retardation showing developmental age of three months. He had a medical history of infantile spasms.

On intraoral examination, overgrown gingival tissue was observed on mandibular left molar area measuring approximately 2.0 × 2.0 × 1.0 cm. Fully erupted mandibular left first molar was covered with overgrown soft tissue and unseen, and mandibular left deciduous second molar was also partially covered with overlying soft tissue. The soft tissue mass overlying was erythematous and ulcerative in appearance and showed spontaneous bleeding (Fig. 1A). The enlarged gingival tissue had dark red color showing hematomatic changes. The patient exhibited poor oral hygiene. Radiographic examination revealed no abnormalities (Fig. 1B). Based on patient's history, clinical evaluation and radiographic assessment, a provisional diagnosis of valproic acid-induced gingival overgrowth superimposed with inflammation was established.

Irrigation with 10 mL of 0.2% chlorhexidine and saline was performed. The parents were instructed to improve the oral hygiene of the patient and to revisit clinic two days later for follow-up. On his second visit, however, the lesion on mandibular left area did not subside at all and the gingiva on maxillary left molar area showed mild gingival swelling and bleeding tendency. The enlarged gingival tissue was irrigated with chlorhexidine and saline, and an oral antibiotic was prescribed for five days. The parents were educated to rinse the lesion with 10 mL of 0.2% chlorhexidine mouthwash and saline twice daily and to maintain strict oral hygiene. He was asked to report back after one week. The tissue in the meantime, however, did not decrease in size and inflammation did not subside. One week after his second visit, the involved teeth, mandibular left deciduous canine, first molar, second molar, showed increased mobility and the affected areas were expanded to the maxillary right side. Considering the patient's limited cooperative ability, gingivectomy under general anesthesia was planned.

Surgical procedure was performed under general anesthesia with respect to four quadrants to remove the overgrowing tissue using surgical blades (Fig. 2). Fibrous bony lesion was detected on the alveolar bone on mandibular left first molar area and facial swelling was observed on mandibular angle area of the same side. Alveolar curettage and drain insertion was done to eliminate all pathological material. The wound was closed with 4-0 sutures.

The tissues excised were fixed in 10% formalin and sent for histological assessment, which revealed an increase in connective tissue and a relative decrease in epithelial thickness. Inflammatory cell infiltration was found in a mixture of dense and loose fibrous connective tissue with extensive hemorrhage and edema (Fig. 3). This confirmed our diagnosis of drug associated gingival enlargement. The bone fragments showed mature cancellous bone with fibrous stroma. Patient was asked to come for check-

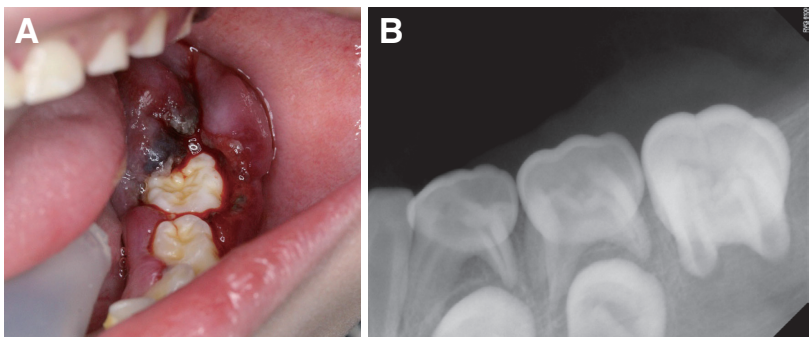

Fig. 1. (A) Intraoral photograph and (B) Periapical radiograph taken on the patient's first visit to the clinic. Gingival overgrowth is observed on mandibular left molar area.

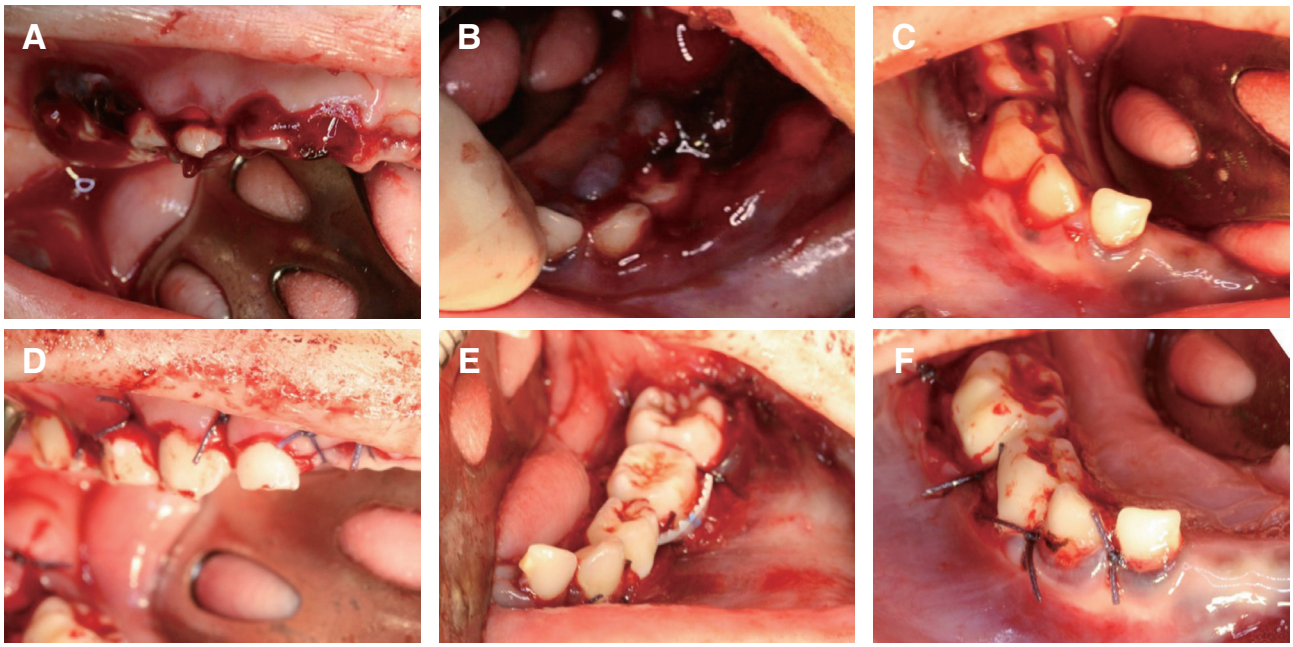

Fig. 2. (A-C) Preoperative intraoral photographs and (D-F) Postoperative intraoral photographs taken in operating room. (A) and (D) show the maxillary right quadrant. (B) and (E) show the mandibular left quadrant. (C) and (F) show the mandibular right quadrant.

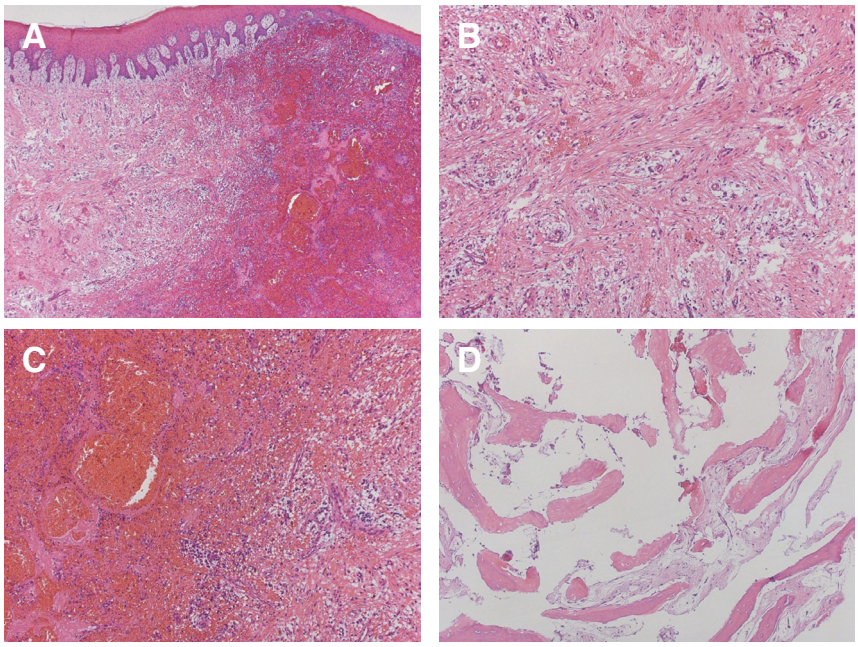

Fig. 3. (A-C) Histopathological examination of gingival overgrowth. (A) Low-power view showing excess fibrous connective tissue and hemorrhage (H-E, X40). (B) Excessive fibrous connective tissue (H-E, X100). (C) Extensive hemorrhage (H-E, X100). (D) Mature cancellous bone with fibrous stroma (H-E, X100).

up after two weeks. Patient was also prescribed anti-inflammatory analgesic drug for management of postoperative pain for five days. Patient was asked to maintain oral hygiene strictly in the surgically treated area, as the treated area was open and raw wound surface.

On examination after two weeks, the overgrowth had subsided almost completely. No further surgical treatment was planned but patient was asked to maintain strict oral hygiene. On examination after six weeks, the mobility of mandibular left teeth entirely disappeared and good oral health was established. The patient exhibited a clinically sound result for five months of follow up period without recurrence.

Ⅲ. Discussion

The patient described herein had Lennox-Gastaut syndrome, which is an intractable form of childhood-onset epilepsy. The syndrome is characterized by a triad of signs including multiple types of epileptic seizures to include tonic, atypical absences, and drop attacks, an interictal EEG showing generalized slow spike wave (1.5 to 2.5 Hz) during awake and paroxysmal fast activity (PFA) during sleep, and slow mental development and/or behavior disturbance.[6] The present patient was taking multiple antiepileptic drugs (AEDs), DepaKOTE (valproate), Inovelon (rufinamide), Keppra (levetiracetam) and phenobarbital, to maintain seizure freedom.

AEDs are widely known to have the potential to cause gingival overgrowth as one of the adverse effects. The prevalence of gingival overgrowth has been shown to vary, from 13 to 50%, in the patients on long-term phenytoin medication[7]. Bharat et al.[8] reported that phenytoin caused gingival overgrowth in 53.6% of children within three months.

Drug-induced gingival overgrowth begins as a firm, nodular enlargement of the interdental papilla, limited to keratinized portions of the gingiva. Fibroblasts in the connective tissue are the target cells. Inflammatory microenvironment is a prerequisite for development of overgrowth because fibroblasts are in an active state when the tissue is inflamed. Local stimuli on the overgrown gingiva bring about inflammatory changes turning the affected area into dark red-colored and easy-to-bleed tissue.

The mechanism of pathogenesis of gingival overgrowth has not been thoroughly disclosed. The associated drugs affect cellular calcium metabolism and calcium influx modulates cellular production of collagenase. Fibroblasts in the patients medicated with these drugs may produce an inactive form of collagenase, which cause an increase in extracellular matrix[2]. Kato et al.[9] suggested that TNF-α and phenytoin together cause impairment in collagen metabolism by suppression of enzymatic degradation with MMPs/TIMP-1 and integrin-mediated endocytosis. Recent studies report that gingival overgrowth is induced by the disruption of homeostasis in collagen synthesis and degradation of gingival connective tissue, primarily due to the inhibition of collagen phagocytosis of gingival fibroblasts[4].

The patient herein was taking valproic acid, which is used to treat seizure disorders and certain psychiatric conditions (e.g., manic phase of bipolar disorder, schizophrenia) and prevent migraine headaches. The pharmacodynamics of the agent is not clearly known, but it is supposed to have anticonvulsant effects associated with increased gamma-aminobutyric acid (GABA) in brain.

To our knowledge, there have been only a few case reports in the literature concerning valproate-induced gingival enlargement. A case of gingival overgrowth occurred in a 14-year-old girl, eighteen months after the taking valproate, was reported by Behari[10]. Joshipura[11] reported an unusual case in which the patient not having any gingival problem in spite of taking phenytoin for one year developed gingival overgrowth after taking sodium valproate within six months. Banita et al.[12] reported a case of a neonate with fetal valproate syndrome.

Histologic examination revealed increased volume of fibrotic connective tissue. According to Kataoka et al.[13,14], drug-induced gingival overgrowth is shown to be induced by the excessive accumulation of type I collagen in connective tissue in rats.

Abundant red blood cells and inflammatory cells were observed in gingival connective tissue and intermittent discontinuation of epithelium was seen. It is thought that the increased volume of soft tissue has interfered with the occlusion of deciduous molars on the affected side and continuous stimuli by maxillary teeth have made the lesion worse resulting in ulceration, hemorrhage and inflammatory changes.

The ideal treatment for medically induced gingival enlargement is discontinuation of medication. This approach, however, is often impractical. Reducing polytherapy and employing monotherapy with lowest effective dose may contribute to avoid and minimize drug-induced gingival overgrowth[7]. Definitive treatment is surgical removal of excess gingival tissue, especially in patients with severe gingival overgrowth that compromise esthetics and function. The use of carbon dioxide laser surgery is becoming common in gingivectomy due to advantages in postoperative hemostasis[15]. Although an operation provides immediate and dramatic results, gingival overgrowth has the potential to recur when the causative medication must be used for ongoing therapy. In some patients, periodic surgical reduction of soft tissue is necessary and good oral hygiene can decrease or prevent the gingival overgrowth[16].

Ⅳ. Summary

Drug-induced gingival overgrowth is an unusual gingival enlargement which is caused by unwanted effects of systemic medication. In the case described herein, valproate-induced gingival overgrowth occurred in all four quadrants exhibiting ulcerated and hemorrhagic manifestations in a patient with Len-

nox-Gastaut syndrome. When gingival enlargement does not subside with nonsurgical treatments, surgical procedure is to be performed. Postoperative management of oral hygiene is critical to prevent recurrence.

REFERENCES

1. Newman M, Takei H, Klokkevold P, Carranza F : Carranza's clinical periodontology, 11th ed., Elsevier/Saunders, 2012.
2. Brunet L, Miranda J, Farre M, et al. : Gingival enlargement induced by drugs. Drug Saf, 15:219-231, 1996.
3. Rees TD, Levine RA : Systematic drugs as a risk factor for periodontal disease initiation and progression. Compendium, 16:20, 22, 26 passim; quiz 42, 1995.
4. Dongari A, McDonnell HT, Langlais RP : Drug-induced gingival overgrowth. Oral Surg Oral Med Oral Pathol, 76:543-548, 1993.
5. Dahllof G, Preber H, Eliasson S, et al. : Periodontal condition of epileptic adults treated long-term with phenytoin or carbamazepine. Epilepsia, 34:960-964, 1993.
6. Markand ON : Lennox-Gastaut syndrome (childhood epileptic encephalopathy). J Clin Neurophysiol, 20:426-441, 2003.
7. St Louis EK : Minimizing AED adverse effects: improving quality of life in the interictal state in epilepsy care. Curr Neuropharmacol, 7:106-114, 2009.
8. Suneja B, Chopra S, Thomas AM, Pandian J : A clinical evaluation of gingival overgrowth in children on antiepileptic drug therapy. J Clin Diagn Res, 10:Zc32-36, 2016.
9. Kato T, Okahashi N, Ohno T, et al. : Effect of phenytoin on collagen accumulation by human gingival fibroblasts exposed to TNF-alpha in vitro. Oral Dis, 12:156-162, 2006.
10. Behari M : Gingival hyperplasia due to sodium valproate. J Neurol Neurosurg Psychiatry, 54:279-280, 1991.
11. Joshipura V : Sodium valproate induced gingival enlargement with pre-existing chronic periodontitis. J Indian Soc Periodontol, 16:278-281, 2012.
12. Rodriguez-Vazquez M, Carrascosa-Romero MC, Pardal-Fernandez JM, Iniesta I : Congenital gingival hyperplasia in a neonate with foetal valproate syndrome. Neuropediatrics, 38:251-252, 2007.
13. Kataoka M, Shimizu Y, Kunikiyo K, et al. : Cyclosporin A decreases the degradation of type I collagen in rat gingival overgrowth. J Cell Physiol, 182:351-358, 2000.
14. Kataoka M, Shimizu Y, Kunikiyo K, et al. : Nifedipine induces gingival overgrowth in rats through a reduction in collagen phagocytosis by gingival fibroblasts. J Periodontol, 72:1078-1083, 2001.
15. Dongari-Bagtzoglou A : Drug-associated gingival enlargement. J Periodontol, 75:1424-1431, 2004.
16. Fitchie JG, Comer RW, Hanes PJ, Reeves GW : The reduction of phenytoin-induced gingival overgrowth in a severely disabled patient: a case report. Compendium, 10:314, 317-320, 1989.