Drug-influenced Gingival Enlargement: Overview of the Clinical Features and Assessment Methods

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Abstract: Drug-influenced gingival enlargement is an unwanted effect of the gingiva affecting patients' aesthetic as well as oral hygiene procedures. The presentation of the enlargement may range from mild to severe by which the chewing function could also be affected. Patients usually were not aware of this condition until they feel discomfort, thus seek for treatment. This review will discuss the overview of common drugs that influence gingival enlargement, its clinical features, previous and current methods of assessment to determine the severity of the gingival enlargement. The review will serve as a guide for clinician in making diagnosis and treatment plan of such condition.

Keywords: Gingival enlargement, Drug-induced gingival overgrowth, Calcium channel blocker, Immunosuppressant, Anticonvulsant.

INTRODUCTION

Drug-influenced gingival enlargement is an unwanted effect occurring on the periodontium that commonly associated with medications. This condition may affect the aesthetics, mastication, speech and oral hygiene measures that could leads to further periodontal inflammation [1, 2]. Many terms implied to these medication-related conditions labelled as 'gingival overgrowth', 'gingival hyperplasia' and recently known as 'gingival enlargement' in new classification of periodontal disease [3]. There is an increasing number of medications shown to induce gingival conditions whereby currently 20 prescriptions have been reported [4]. The drugs that commonly being associated with gingival enlargement were includes anticonvulsants such as phenytoin and sodium valproate; certain calcium channel blockers (*e.g*, nifedipine, verapamil, diltiazem, amlodipine, felodipine); immunosuppressants such as cyclosporin A and tacrolimus [5, 6]. The etiological and mechanism of drug influenced gingival enlargement has not fully determined yet and thought to be multifactorial and response to various interactions between the host and environment. This review discusses the nature and use of the associated drugs, key clinical and histopathological features of the gingival enlargement as well as the methods used for gingival assessment. Moreover, this review could be a basis of oral health awareness among physicians for early management of patients that affected by those drugs implicates gingival condition.

ANTICONVULSANTS

Anticonvulsants aim to treat epilepsy, a group of central nervous system disorders which have in common the occurrence of sudden and transitory episodes (seizures) of abnormal phenomena of motor (convulsions), sensory, autonomic or psychic origin with or without loss of consciousness due to abnormal central nervous system activity. Such seizures are nearly always associated with abnormal discharges recorded on the electroencephalogram (Commission on Classification and Terminology of the International League Against Epilepsy, 1981). There are 3 generations of anticonvulsant drugs as shown in Table **1**. Anticonvulsants include phenytoin, phenobarbitone, primidone (which is converted into phenobarbitone in the liver), carbamazepine, ethosuximide and valproic acid. In the treatment of status epilepticus, the benzodiazepines, especially diazepam and midazolam are a drug of choice. Carbamazepine usually used in dentistry especially in the treatment of trigeminal, glossopharyngeal and post-herpetic neuralgia [7]. Basically, for preventing convulsions, the drugs have two general modes of action which are firstly; the drugs can act on pathologically altered neurons when subjected to seizure foci and prevent or reduce excessive discharges of them. Secondly, anticonvulsants reduce the spread of excitation from seizure foci and this prevent detonation and disruption of function in another normal neuron [8].

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Table 1: Anticonvulsant Drugs. Adopted from Brunet *et al*. in 2001 [9]

First Generation	Phenytoin Phenobarbital (Phenobarbitone)
Second Generation	Carbamazepine Valproic acid (Sodium Valproate)
Third Generation	Gabapentin Lamotrigine Vigabatrin

However, those drugs indirectly affect the gingival tissues. Phenytoin becomes the most drug affecting gingival enlargement in this anticonvulsant class which usually prominent in the first 3 month after phenytoin dosage prescribed and most rapidly occur in the first year of taking medication [10]. While Dahloff and Modeer in 1986 had observed the clinical onset of gingival overgrowth was as early as 1 month after taking phenytoin and reach maximum severity 2 to 18 months later.Yet, the effect had reduced during the second year on medication. The incidence of phenytoin-induced gingival enlargement ranged from 1% to 93% with an average approximating 50% occurrence of gingival enlargement [7, 9]. The relationship between daily dose duration of use and blood or salivary levels of phenytoin have been related to the presence and degree of gingival enlargement but several other studies have failed to detect such correlation [11, 12].

CALCIUM CHANNEL BLOCKERS

Calcium channel blockers (CCB) have been widely prescribed for the treatment of various cardiovascular diseases including angina pectoris, cardiac arrhythmias, coronary spasm, and mostly hypertension [13]. CCB is among five major pharmacological classes of antihypertensive drugs that include beta-blockers, diuretics angiotensin converting enzyme inhibitors, and angiotensin II receptor antagonists [14]. CCB also known as calcium antagonist act to disrupt the movement of the calcium through the calcium channels, thus relax and widen the blood vessel leading to decrease in blood pressure. However, CCB such as nifedipine and amlodipineare commonly associated with gingival enlargement [13]. Table **2** shows two classes of CCB; dihydropyridines and non-dihydropyridines.

The common side effects of calcium channel blockers include headache, dizziness, facial flushing and oedema [15]. Gingival enlargement was first reported in association with nifedipine [16] and later was also described with verapamil, diltiazem and amlodipine usage [17-19]. Most of the published reports demonstrated nifedipine and amlodipine induced gingival overgrowth. In rat model, a minimum plasma concentration of 800ng/ml of nifedipine resulted in gingival enlargement and that degree of enlargement depended on increased concentrations above this threshold value [20].

Table 2: Classes of Calcium Channel Blockers (Adopted from 132nd Edition, MIMS, 2013)

Calcium Channel Blockers	
Dihydropyridines	**Non-Dihydropyridines**
Amlodipine,	Diltiazem,
Nifedipine,	Diltiazem SR,
Felodipine,	Verapamil,
Isradipine,	Verapamil SR
Lacidipine,	
Lercanidipine	

The prevalence of gingival enlargement influenced by calcium channel blockers were range from 6% to 83% in Caucasian population [2, 21-23]. There is scarce evidence of the gingival enlargement among Asian population. In Malaysia, there were only two cases been reported [24, 25]. Previous studies found that the prevalence of drug influenced gingival enlargement in relation to diltiazem, amlodipine, verapamil were 74%, 3.3% and 21% respectively [19, 21, 26-28]. Recently, Gopal *et al.* (2018) reported that from 16 subjects taking β blockers, 2 diltiazem and 5 losartan in their study, none of patients manifested drug induced gingival enlargement.

IMMUNOSUPPRESSANTS

Immunosuppressants is mainly used to lower the risk of rejection post-transplantation of organ donation. It acts on various components of the immune system causing selective inhibition and suppression [7]. Cyclosporin, azathioprine and tacrolimus are some examples of immunosuppressants. Cyclosporin A was introduced in human organ transplantation for more than few decades to prevent organ rejection which 50% success rate. From every kidney allograft performed, half failed within 1 to 3 years. The common adverse effects of this drug include nephrotoxicity,

hypertension, hepatotoxicity and neurotoxicity. Whereas the oral side effects of cyclosporin A include the rare lingual fungiform papillae hypertrophy (LFPH) and also gingival enlargement [29]. The incidence of cyclosporin-influenced gingival enlargement was about 25% to 70% with higher in females than males [30-33]. Past study has shown that severity of cyclosporin-influenced gingival enlargement was significantly related to the plasma concentration (≤400ng/ml) of the drug [34]. Drug influenced gingival enlargement in association with tacrolimus has also been reported particularly when it is administered in combination with amlodipine [35].

CLINICAL AND HISTOPATHOLOGICAL FEATURES OF DRUG-INFLUENCED GINGIVAL ENLARGEMENT

Drug influenced gingival enlargement usually develops in a susceptible individual within a few months of starting the medications as early of 1 months. Also, it is more frequently found adjacent to the labial surfaces of the anterior segments and usually confined to the attached gingiva between the teeth but may extend coronally, interfering with aesthetics, speech, and mastication [36]. There is a tendency for drug influenced gingival enlargement to affect posterior teeth also but rarely pronounce compared to anterior teeth [37]. As the tissue enlarges it develops a characteristically thickened and lobulated appearance [38]. It must be differentiated with other gingival lesion such as inflammatory enlargement, pyogenic granuloma, peripheral giant cell granuloma, systemic disease influenced gingival enlargement, neoplastic gingival enlargement and others by history of patient and clinical appearance. The epithelial surface is usually smooth, fibrotic but can be nodular in some drugs (Figure **1**).

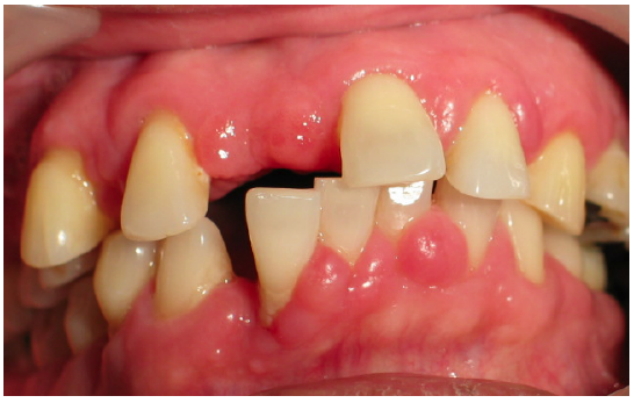

Figure 1: Clinical appearance of drug-influenced gingival enlargement in hypertensive patient taking amlodipine.

In human gingivectomy samples analysis of drug influenced gingival enlargement, it was found that possible role of connective tissue growth factor (CTGF) in promoting development of fibrotic lesions in the gingiva. The findings showed elevation of CTGF level in drug influenced gingival enlargement in patients taking phenytoin and nifedipine to a lesser extent. Also very little increased of CTGF in cyclosporin A-influenced gingival enlargement [39]. However, if the lesion is associated with the presence of periodontal disease, the tissues may appear inflamed, red or purplish in colour, and bleed profusely upon probing [40].

Gingival enlargement tends to be more severe in areas where plaque accumulates, such as at the edges of restorations and around orthodontic appliances but it rarely seen in edentulous area. Clinical parameters such as the standard of oral hygiene, drug dosage, serum and salivary levels have some relationship to the incidence of gingival enlargement [38]. There was increased epithelial thickness observed in drug influenced gingival enlargement and is associated with increased mitotic activity, especially in the spinous layer of oral epithelium [41].

An ultrastructural study of drugs-influenced gingival enlargement showed that the increase in gingival tissue is based on connective tissue response rather than epithelial cell layer involvement. Histologically, drug-influenced gingival enlargement associated with excessive accumulation of extracellular matrix protein such as collagen or amorphous ground substance. Besides, variable thickness of parakeratinized epithelium covers the connective tissue stroma and epithelial ridges may penetrate deep into connective tissue, creates irregularly arranged of collagen fibres [42]. Evidence also supports that connective tissue is an essential feature in the pathogenesis of drug-influenced gingiva enlargement with increase in connective tissue matrix. Gingival fibroblasts produces collagen, with specific rise in the level of type I procollagen which is controlled by synthesis and release of matrix metalloproteinases and tissue inhibitor of metalloproteinases [43]. Hence, from the findings regarding the tissue layer affected by inducing drugs, it was concluded that histopathological drug-influenced gingival enlargement involves both layers which are oral epithelium as well as connective tissue layer.

Furthermore, Kantarci *et al*. in 2011 [44] stated that there are significantly higher numbers of basement membrane discontinuities in gingival enlargement tissues and it may contain epithelial-like cells. Disrupted basal membrane structures in gingival

Table 3: Indices for Assessment of Gingival Enlargement

Index	Methods of Assessment	Descriptions
Angelopoulos and Goaz in 1972 [10]	Direct/ Clinical	Grade 0: No hyperplasia; normal gingiva. Grade 1: The hyperplastic gingiva covered the cervical third or less of the anatomic crown of the anterior teeth. Grade 2: The hyperplastic gingiva extended anywhere in the middle third of the anatomic crowns of the anterior teeth. Grade 3: The hyperplastic gingiva covered more than two thirds of the anatomic crowns of the anterior teeth.
Seymour Index [46]	Indirect/ study model cast	Gingival enlargement grading on study models on the buccal and lingual/palatal papillae associated with the six most anterior upper and lower teeth. The assessment was based on a 3-dimensional study of plaster casts and evaluates on 5 gingival units of the upper and lower anterior segments (from the midpoint of the right canine to the midpoint of the left canine). The degree of gingival thickening on both labial and lingual aspects grading as follows: Grade 0: normal Grade 1: thickening from the normal up to 2 mm Grade 2: thickening from the normal greater than 2 mm Gingival encroachments on adjacent tooth surfaces were measured from proximal surface to the free gingival margin and graded from 0 to 3 which later modified by Andrew *et al*. in 2014 to allow measurement in millimetres (mm).
Clinical Index for DIGO [49]	Direct/ Clinical	This index assessing the whole dentition anterior and posterior segments by examining the lingual and facial interdental papillae and the grading as follows: Grade 0: No overgrowth, slight stippling, and no increase in density or size of the gingiva. Grade 1: Early overgrowth, evidenced by increased in density of the gingiva with marked stippling and granular appearance, tip of the papilla is rounded, and probing depth is ≤ 3mm. Grade 2: Moderate overgrowth, evidenced by increase in the size of the papilla, contour of gingival margin is concave or straight, gingival enlargement has a buccolingual dimension of up to 2mm, papilla is somewhat retractable, and probing depth is ≤ 6mm. Grade 3: Marked overgrowth, with encroachment of the gingiva onto the clinical crown, gingival margin contour is convex rather than concave, gingival enlargement has a buccolingual dimension of approximately ≥ 3mm, papilla is retractable, and probing depth is > 6mm. Grade 4: Severe overgrowth, characterized by a profound thickening of the gingiva, large part of the clinical crown is covered, buccolingual dimension is approximately 3mm, papilla is retractable and probing depth is > 6mm.
Miranda-Brunet (MB) Index [47]	Direct/ Clinical	Measurement was based on the size of the papilla from the enamel surface, at the interdental contact point to the outer papillary surface. Two scores were obtained, one for the buccal papilla and another for the lingual/palatal papilla, according to the following criteria: The whole mouth assesses clinically anterior and posterior areas, and buccal and lingual/palatal surfaces in this index. An average mean grade calculated after the scores producible as below: Grade 0: Papillary thickness of less than 1 mm Grade 1: Papillary thickness between 1 mm and 2 mm Grade 2: Papillary thickness > 2 mm
Nodullary Papillary Index by Miranda *et al*. [48]	Direct/ Clinical	A combination of GO index by Miller and Dammin 1992 and MB Index. This modification records the 2 components of gingival enlargement at any site, horizontal nodular enlargement (MB index) in the interdental papilla and vertical (GO index) gingival enlargement.
Andrew *et al*. Index [2]	Indirect/ study model cast	Slight modification of the Seymour Index. The grading are as follows: Grade 0: Normal gingiva Grade 1: Less than 2 mm increase in size Grade 2: 2 mm to 4 mm increase in size Grade 3: Nodular growth greater than 4 mm

enlargement tissues is assisted by a discontinuous collagen type IV expression pattern and decreased of laminin-5. These findings support the hypothesis that epithelial plasticity and epithelial to mesenchymal transition promote gingival enlargement, resulting in compromised basal membrane structure and increased interaction between epithelial and connective tissue layer in pathogenesis of drug-influenced gingival enlargement [44, 45]. In addition, inflammation on gingival enlargement area with focal accumulations of infiltrating inflammatory cells particularly plasma cells resulted with highly vascularized connective tissue and this condition may lead to further periodontal destruction and difficulty in teeth cleaning on that area.

ASSESSMENT OF DRUG-INFLUENCED GINGIVAL ENLARGEMENT

There are few indices to assess the severity of drug-influenced gingival enlargement. In the past four decades, gingival enlargement was originally described by Angelopoulos and Goaz in 1972 [10] and later modified by Miller and Damn in 1992 [28] known as gingival overgrowth (GO) index. Seymour *et al*. had come out with indirect technique by measuring gingival enlargement on study model cast [46]. GO index was then modified by Miranda *et al*. in 1998 known as Miranda-Brunet (MB) index [47] and later on in 2001 known as Nodullary Papillary index [48]. This method determines the severity of gingival enlargement by grading the mean of GO index and MB index. In the same time, Ingles *et al*. in 1999 [49] had introduced the Clinical Index (CI) for Drug-induced Gingival Overgrowth (DIGO). This index does not require diagnostic casts and intraoral photographs, yet, provide some indication of the severity of the lesions as well as aid in deciding appropriate treatment intervention. Meanwhile, the indirect technique proposed by Seymour *et al*. in 1985 was later modified by Andrew and coworkers in 2014 [2]. All the indices are summarized in Table **3**.

CONCLUSION

The common drug-influenced gingival enlargement has almost similar in their clinical as well as histopathological appearance. Proper diagnosis with the available assessment methods for gingival enlargement would benefits both clinician and the patients as it provides more efficient treatment modalities that may increase oral health awareness, thus improve patients' quality of life.

REFERENCES

[1] Amit B, Shalu B. Gingival enlargement induced by anticonvulsants, calcium channel blockers and immunosuppressants: a review. IRJP 2012; 3: 116-119.

[2] Andrew W, Evelyn W, Francis M, Mark J, Mark C. Pattern of gingival overgrowth among patients on antihypertensive pharmacotherapy at a Nairobi hospital in Kenya. Open Journal of Stomatology 2014; 4: 169. https://doi.org/10.4236/ojst.2014.44025

[3] Murakami S, Mealey BL, Mariotti A, Chapple IL. Dental plaque–induced gingival conditions. Journal of Clinical Periodontology 2018; 45: S17-S27. https://doi.org/10.1111/jcpe.12937

[4] Gupta N, Goyal L, Gupta N. Periodontal Management of Phenytoin Induced Gingival Enlargement: A Case Report. J Dent Health Oral Disord Ther 2017; 8: 00271.

[5] Preshaw PM. Oral contraceptives and the periodontium. Periodontology 2000 2013; 61: 125-159. https://doi.org/10.1111/j.1600-0757.2011.00399.x

[6] Brown RS, Arany PR. Mechanism of drug-induced gingival overgrowth revisited: a unifying hypothesis. Oral Dis 2015; 21: e51-61. https://doi.org/10.1111/odi.12264

[7] Seymour R, Heasman P. Drugs and the periodontium. Journal of Clinical Periodontology 1988; 15: 1-16. https://doi.org/10.1111/j.1600-051X.1988.tb01549.x

[8] Richens A. Clinical pharmacokinetics of phenytoin. Clinical Pharmacokinetics 1979; 4: 153-169. https://doi.org/10.2165/00003088-197904030-00001

[9] Brunet L, Miranda J, Roset P, Berini L, Farre M, Mendieta C. Prevalence and risk of gingival enlargement in patients treated with anticonvulsant drugs. European Journal of Clinical Investigation 2001; 31: 781-788. https://doi.org/10.1046/j.1365-2362.2001.00869.x

[10] Angelopoulos A, Goaz P. Incidence of diphenylhydantoin gingival hyperplasia. Oral Surgery, Oral Medicine, Oral Pathology 1972; 34: 898-906. https://doi.org/10.1016/0030-4220(72)90228-9

[11] Modéer T, Dahllöf G, Theorell K. Oral health in non-institutionalized epileptic children with special reference to phenytoin medication. Community Dentistry and Oral Epidemiology 1986; 14: 165-168. https://doi.org/10.1111/j.1600-0528.1986.tb01524.x

[12] Hassel, Hefti. Drug-induced gingival overgrowth: old problem. Critical reviews in oral biology and medicine: an official publication of the American Association of Oral Biologists. Critical Review in Oral Biology and Oral Medicine 1991; 2: 103-137.

[13] Gopal S, Joseph R, Santhosh VC, Kumar VVH, Joseph S, Shete AR. Prevalence of gingival overgrowth induced by antihypertensive drugs: A hospital-based study. Journal of Indian Society of Periodontology 2015; 19: 308. https://doi.org/10.4103/0972-124X.153483

[14] Laurent S. Antihypertensive drugs. Pharmacological Research 2017; 124: 116-125. https://doi.org/10.1016/j.phrs.2017.07.026

[15] Marshall RI, Bartold PM. A clinical review of drug-induced gingival overgrowths. Australian Dental Journal 1999; 44: 219-232. https://doi.org/10.1111/j.1834-7819.1999.tb00224.x

[16] Lederman D, Lumerman H, Reuben S, Freedman PD. Gingival hyperplasia associated with nifedipine therapy: report of a case. Oral Surgery, Oral Medicine, Oral Pathology 1984; 57: 620-622. https://doi.org/10.1016/0030-4220(84)90283-4

[17] Cucchi G. Gingival hyperplasia caused by verapamil. Ital J Cardiol 1985; 15: 556-557.

[18] Colvard M, Bishop J, Weissman D, Gargiulo A. Cardizem induced gingival hyperplasia: a report of two cases. Periodontal case reports: a publication of the Northeastern Society of Periodontists 1986; 8: 67-68.

[19] Seymour R, Ellis J, Thomason J, Monkman S, Idle J. Amlodipine-induced gingival overgrowth. Journal of Clinical Periodontology 1994; 21: 281-283. https://doi.org/10.1111/j.1600-051X.1994.tb00318.x

[20] Nishikawa S, Nagata T, Morisaki I, Oka T, Ishida H. Pathogenesis of drug-induced gingival overgrowth. A review of studies in the rat model. Journal of Periodontology 1996; 67: 463-471. https://doi.org/10.1902/jop.1996.67.5.463

[21] Ellis JS, Seymour RA, Steele JG, Robertson P, Butler TJ, Thomason JM. Prevalence of gingival overgrowth induced by calcium channel blockers: a community-based study. Journal of Periodontology 1999; 70: 63-67. https://doi.org/10.1902/jop.1999.70.1.63

[22] Beaumont J, Chesterman J, Kellett M, Durey K. Gingival overgrowth: Part 1: aetiology and clinical diagnosis. Br Dent J 2017; 222: 85-91. https://doi.org/10.1038/sj.bdj.2017.71

[23] Umeizudike KA, Olawuyi AB, Umeizudike TI, Olusegun-Joseph AD, Bello BT. Effect of calcium channel blockers on gingival tissues in hypertensive patients in Lagos, Nigeria: A pilot study. Contemporary Clinical Dentistry 2017; 8: 565. https://doi.org/10.4103/ccd.ccd_536_17

[24] Taib H, Ali TBT, Kamin S. Amlodipine-induced gingival overgrowth: a case report. Archives of Orofacial Sciences 2007; 2: 61-64.

[25] Asari ASM. The Expert Says Current Concept in Gingival Overgrowth. Editorial Advisory Board 2007; 28: 107-111.

[26] Miranda J, Brunet L, Roset P, Berini L, Farré M, Mendieta C. Prevalence and risk of gingival overgrowth in patients treated with diltiazem or verapamil. Journal of Clinical Periodontology 2005; 32: 294-298. https://doi.org/10.1111/j.1600-051X.2005.00662.x

[27] Bowman JM, Levy BA, Grubb RV. Gingival overgrowth induced by diltiazem: a case report. Oral Surgery, Oral Medicine, Oral Pathology and Oral Radiology 1988; 65: 183-185. https://doi.org/10.1016/0030-4220(88)90163-6

[28] Miller CS, Damm DD. Incidence of Verapamil-Induced Gingival Hyperplasia in a Dental Population. Journal of Periodontology 1992; 63: 453-456. https://doi.org/10.1902/jop.1992.63.5.453

[29] Rateitschak-Plüss E, Hefti A, Lörtscher R, Thiel G. Initial observation that cyclosporin-A induces gingival enlargement in man. Journal of Clinical Periodontology 1983; 10: 237-246. https://doi.org/10.1111/j.1600-051X.1983.tb01272.x

[30] Wysocki GP, Gretzinger HA, Laupacis A, Ulan RA, Stiller CR. Fibrous hyperplasia of the gingiva: a side effect of cyclosporin A therapy. Oral Surgery, Oral Medicine, Oral Pathology 1983; 55: 274-278. https://doi.org/10.1016/0030-4220(83)90327-4

[31] Seymour R, Smith D. The effect of a plaque control programme on the incidence and severity of cyclosporin-induced gingival changes. Journal of Clinical Periodontology 1991; 18: 107-110. https://doi.org/10.1111/j.1600-051X.1991.tb01698.x

[32] Daley T, Wysocki G, Day C. Clinical and pharmacologic correlations in cyclosporine-induced gingival hyperplasia. Oral Surgery, Oral Medicine, Oral Pathology 1986; 62: 417-421. https://doi.org/10.1016/0030-4220(86)90291-4

[33] Tyldesley W, Rotter E. Gingival hyperplasia induced by cyclosporin-A. British Dental Journal 1984; 157: 305. https://doi.org/10.1038/sj.bdj.4805474

[34] Seymour R, Smith D, Rogers S. The comparative effects of azathioprine and cyclosporin on some gingival health parameters of renal transplant patients. Journal of Clinical Periodontology 1987; 14: 610-613. https://doi.org/10.1111/j.1600-051X.1987.tb01524.x

[35] Bharti V, Bansal C. Drug-induced gingival overgrowth: the nemesis of gingiva unravelled. Journal of Indian Society of Periodontology 2013; 17: 182. https://doi.org/10.4103/0972-124X.113066

[36] Missouris G, Kalaitzidis R, Cappuccio F, MacGregor G. Gingival hyperplasia caused by calcium channel blockers. Journal of Human Hypertension 2000; 14: 155. https://doi.org/10.1038/sj.jhh.1000954

[37] Smitha Rani Thada VR, Keerthilatha MP. Unusual Clinical Presentation of Generalised Gingival enlargement. International Journal of Collaborative Research on Internal Medicine and Public Health 2012; 4: 240-254

[38] Taylor BA. Management of drug-induced gingival enlargement. Australian Prescriber 2003; 26: 11-13. https://doi.org/10.18773/austprescr.2003.007

[39] Uzel MI, Kantarci A, Hong H-H, Uygur C, Sheff MC, Firatli E, Trackman PC. Connective tissue growth factor in drug-induced gingival overgrowth. Journal of Periodontology 2001; 72: 921-931. https://doi.org/10.1902/jop.2001.72.7.921

[40] Hallmon WW, Rossmann JA. The role of drugs in the pathogenesis of gingival overgrowth. A collective review of current concepts. Periodontology 2000 1999; 21: 176-196. https://doi.org/10.1111/j.1600-0757.1999.tb00175.x

[41] Hall P, Levison D, Woods A, Yu CW, Kellock D, Watkins J, Barnes D, Gillett C, Camplejohn R, Dover R. Proliferating cell nuclear antigen (PCNA) immunolocalization in paraffin sections: An index of cell proliferation with evidence of deregulated expression in some, neoplasms. The Journal of Pathology 1990; 162: 285-294. https://doi.org/10.1002/path.1711620403

[42] Dongari-Bagtzoglou A. Research, Science and therapy committee, american academy of periodontology. Drug-associated gingival enlargement. J of Periodontology 2004; 75: 1424-1431. https://doi.org/10.1902/jop.2004.75.10.1424

[43] Schincaglia G, Forniti F, Cavallini R, Piva R, Calura G, Senno L. Cyclosporin-A increases type I procollagen production and mRNA level in human gingival fibroblasts in vitro. Journal of Oral Pathology & Medicine 1992; 21: 181-185. https://doi.org/10.1111/j.1600-0714.1992.tb00098.x

[44] Kantarci A, Nseir Z, Kim Y-S, Sume S, Trackman P. Loss of basement membrane integrity in human gingival overgrowth. Journal of Dental Research 2011; 90: 887-893. https://doi.org/10.1177/0022034511404703

[45] Sume SS, Kantarci A, Lee A, Hasturk H, Trackman PC. Epithelial to mesenchymal transition in gingival overgrowth. The American Journal of Pathology 2010; 177: 208-218. https://doi.org/10.2353/ajpath.2010.090952

[46] Seymour R, Smith D, Turnbull D. The effects of phenytoin and sodium valproate on the periodontal health of adult epileptic patients. Journal of Clinical Periodontology 1985; 12: 413-419. https://doi.org/10.1111/j.1600-051X.1985.tb01377.x

[47] Miranda J, Brunet LI, Roset PN, Farré M, Berini L, Mendieta C. Prevalence and risk for gingival enlargement induced by calcium channel blockers (abstract). Int J Dent 1998; 48: 450

[48] Miranda J, Brunet L, Roset P, Berini L, Farré M, Mendieta C. Prevalence and risk of gingival enlargement in patients treated with nifedipine. Journal of Periodontology 2001; 72: 605-611. https://doi.org/10.1902/jop.2001.72.5.605

[49] Ingles E, Rossmann JA, Caffesse RG. New clinical index for drug-induced gingival overgrowth. Quintessence Int 1999; 30: 467-473.

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