ISSN 1949-8462 (online)

World Journal of *Cardiology*

World J Cardiol 2021 April 26; 13(4): 68-116

Published by Baishideng Publishing Group Inc

World Journal of Cardiology

Contents

Monthly Volume 13 Number 4 April 26, 2021

OPINION REVIEW

EVIDENCE-BASED MEDICINE

META-ANALYSIS

CASE REPORT

World Journal of Cardiology

Monthly Volume 13 Number 4 April 26, 2021

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Cardiology*, Viktor Čulić, MD, MSc, PhD, Associate Professor, Senior Scientist, Department of Cardiology, University Hospital Centre Split, Split 21000, Croatia. viktor.culic@st.t-com.hr

AIMS AND SCOPE

The primary aim of *World Journal of Cardiology* (*WJC*, *World J Cardiol*) is to provide scholars and readers from various fields of cardiology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJC mainly publishes articles reporting research results and findings obtained in the field of cardiology and covering a wide range of topics including acute coronary syndromes, aneurysm, angina, arrhythmias, atherosclerosis, atrial fibrillation, cardiomyopathy, congenital heart disease, coronary artery disease, heart failure, hypertension, imaging, infection, myocardial infarction, pathology, peripheral vessels, public health, Raynaud's syndrome, stroke, thrombosis, and valvular disease.

INDEXING/ABSTRACTING

The *WJC* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, Scopus, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: *Jia-Hui Li*; **Production Department Director:** *Xiang Li*; **Editorial Office Director:** *Ya-Juan Ma.*

NAME OF JOURNAL
World Journal of Cardiology

ISSN
ISSN 1949-8462 (online)

LAUNCH DATE
December 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Ramdas G Pai, Dimitrios Tousoulis, Marco Matteo Ciccone

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1949-8462/editorialboard.htm

PUBLICATION DATE
April 26, 2021

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Cardiology

Submit a Manuscript: https://www.f6publishing.com

World J Cardiol 2021 April 26; 13(4): 68-75

DOI: 10.4330/wjc.v13.i4.68

ISSN 1949-8462 (online)

OPINION REVIEW

Drug-induced gingival overgrowth in cardiovascular patients

Lucija Bajkovec, Anna Mrzljak, Robert Likic, Ivan Alajbeg

ORCID number: Lucija Bajkovec 0000-0002-6727-1353; Anna Mrzljak 0000-0001-6270-2305; Robert Likic 0000-0003-1413-4862; Ivan Alajbeg 0000-0001-7936-2554.

Author contributions: Bajkovec L made contributions to the conception and design of the study, drafted and revised the manuscript critically; Mrzljak A, Alajbeg I and Likic R collected data, drafted and wrote the manuscript; all authors read and approved the final manuscript.

Conflict-of-interest statement: The authors declare no conflict of interest.

Manuscript source: Invited manuscript

Specialty type: Dentistry, oral

Lucija Bajkovec, Institute of Emergency Medicine of Medimurje County, Institute of Emergency Medicine of Međimurje County, Cakovec 40000, Croatia

Anna Mrzljak, Department of Gastroenterology and Hepatology, University Hospital Center Zagreb, Zagreb 10000, Croatia

Anna Mrzljak, School of Medicine, University of Zagreb, Zagreb 10000, Croatia

Robert Likic, Unit for Clinical Pharmacology and TherapeuticsDepartment of Internal Medicine, University Hospital Centre Zagreb, Zagreb 10000, Croatia

Ivan Alajbeg, Department of Oral Medicine, University of Zagreb School of Dental Medicine and University Hospital Centre Zagreb, Zagreb 10000, Croatia

Corresponding author: Anna Mrzljak, FEBG, PhD, Associate Professor, Department of Gastroenterology and Hepatology, University Hospital Center Zagreb, Kispaticeva 12, Zagreb 10000, Croatia. anna.mrzljak@gmail.com

Abstract

Drug-induced gingival overgrowth (DIGO) is a pathological growth of gingival tissue, primarily associated with calcium channel blockers and immunosuppressants. Consequently, it is mainly seen in cardiovascular and transplanted patients. Nifedipine remains the main calcium channel blocker related to the development of this unpleasant side-effect. As for immunosuppress-ants, cyclosporin is the leading causative agent, whereas other drugs from this drug-group, including tacrolimus, have better safety profiles. Accumulated collagen with inflammatory infiltrates is the histological hallmark of this condition. Several factors are involved in the pathogenesis and can increase the risk, such as male gender, younger age, pre-existing periodontal inflammation, and concomitant use of other DIGO-inducing medications. Patients with DIGO may experience severe discomfort, trouble with speech and mastication, pain, and teeth loss, aside from cosmetic implications. Furthermore, these patients also have an increased risk for cardiovascular diseases. The interdisciplinary approach and cooperation with dental care experts are necessary for patient management. Treatment includes discontinuing the drug and switching to one with a better profile, improving oral hygiene, and surgical removal of enlarged tissue. Recognizing the potential of commonly used medications to cause DIGO and its effect on patients' health is necessary for early detection and adequate management of this complication.

Key Words: Drug-induced gingival overgrowth; Calcium channel blocker; Nifedipine;

surgery and medicine

Country/Territory of origin: Croatia

Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: February 7, 2021
Peer-review started: February 7, 2021
First decision: February 28, 2021
Revised: March 1, 2021
Accepted: March 29, 2021
Article in press: March 29, 2021
Published online: April 26, 2021

P-Reviewer: Ciccone MM, Spartalis M
S-Editor: Zhang L
L-Editor: A
P-Editor: Li JH

Calcineurin inhibitor; Cyclosporin; Cardiovascular

Core Tip: Drug-induced gingival overgrowth is a side-effect of the drugs such as calcium channel blockers and immunosuppressants, commonly used in cardiovascular and transplanted patients. The condition is multifactorial and mainly depends on the potential of the used drug to cause gingival changes and the state of oral hygiene. Patients who develop drug-induced gingival overgrowth may experience severe discomfort and pain in addition to troubles with mastication, speech, and maintaining oral hygiene. Since it significantly reduces the quality of life, preventive and curative measures should be implemented as part of a care plan for patients at risk.

Citation: Bajkovec L, Mrzljak A, Likic R, Alajbeg I. Drug-induced gingival overgrowth in cardiovascular patients. *World J Cardiol* 2021; 13(4): 68-75
URL: https://www.wjgnet.com/1949-8462/full/v13/i4/68.htm
DOI: https://dx.doi.org/10.4330/wjc.v13.i4.68

INTRODUCTION

Drug-induced gingival overgrowth (DIGO) is a pathological growth of the gingiva characterized by the accumulation of connective tissue that primarily affects the anterior regions of the maxilla and mandibula[1-3]. The first large DIGO case series was described in 1939, showing DIGO in 68 out of 119 patients treated by antiepileptic drug phenytoin[4].

Since then, various medications showed to be associated with this side-effect[5]. Although more than 20 different drugs are now known to cause DIGO, it most frequently results from calcium channel blockers (CCBs) and immunosuppressants[6,7]. Antiepic drugs (*e.g.*, phenytoin, valproic acid, phenobarbital, vigabatrin) are recognized as a prominent group of medications causing DIGO, although in recent years, cases of DIGO resulting from these drugs were less frequently reported[8].

Cardiovascular and transplanted patients are at particular risk due to the extensive use of CCBs alone or in combination with immunosuppressants[9,10]. Significant variability among patients medicated with the same drugs is observed[1], indicating the importance of additional risk factors involved in the pathogenesis. Genetic factors, male gender, bacterial plaque, and gingival inflammation are associated with increased DIGO risk[11]. Aside from the cosmetic effect, which is the most apparent feature, patients who develop DIGO experience difficulty maintaining oral hygiene, pronunciation, and mastication. Simultaneously, the extensive disease can cause pain and loss of the teeth. As a result, quality of life is reduced significantly[12,13]. Since this side-effect is not rare in a group of cardiovascular patients, oral health needs to be emphasized and included as part of a care plan for patients treated with the drugs mentioned above.

CLINICAL FEATURES AND PATHOGENESIS

DIGO usually starts as painless enlargement of interdental papillae and progresses towards facial and lingual margins, covering the teeth crowns. Fully developed, it forms generalized changes throughout the mouth, affecting the anterior gingiva the most[5], although it can also occur as a localized lesion[14]. A possible explanation for the predominance of lesions in anterior regions could be higher exposure of anterior gingiva to the irritation resulting from plaque[15]. DIGO initially appears as pink, lobulated, and thickened gingival tissue without concomitant inflammation, with no tendency to bleed[5,16]. In its course it becomes inflamed with red or bluish-red discolorations and frequent bleeding[5]. As it progresses, it spreads both vertically and horizontally and affects mastication and speech[14].

In advanced forms, enlarged gingiva may even interfere with the occlusion[5]. Patients with DIGO have problems maintaining oral hygiene, which leads to susceptibility to infections and periodontal disease and may result in the loss of the teeth[14]. A weakened immune system predisposes to more severe periodontal disease and puts patients on immunosuppressants at additional risk[17]. Furthermore, periodontitis may potentially carry a risk for cardiovascular diseases, including myocardial infarction, peripheral artery disease, stroke, and heart failure. In theory, possible mechanisms behind this association could be dissemination of oral pathogens into the bloodstream and invasion of cardiovascular organs and tissues to induce inflammatory response on a local and systemic level[18]. Additionally, periodontitis is associated with endothelial dysfunction, an important factor in atherosclerosis development[18,19]. Aside from the functional impairment and cardiovascular risk, gingival changes also represent a significant esthetic problem for the patients[14].

Etiopathology of DIGO is multifactorial and not fully understood[2,20]. Genetic factors (cytochrome P450, HLA, and MDR1 gene polymorphisms) influence the interindividual difference in gingival response to DIGO-inducing drugs and could have a role in identifying patients at risk[2,21,22]. The main histological finding in DIGO is the accumulation of collagen in the gingiva's extracellular matrix, along with the infiltration of inflammatory cells[1]. Most of the DIGO-inducing drugs act as inhibitors of calcium ion influx[23]. An inhibited influx of cations into fibroblasts causes a decrease in cation-dependent folic acid uptake. Folic acid is necessary for the proper function of matrix metalloproteinases, which activate collagenase. With no collagenase, there is no collagen breakdown, and it accumulates in connective tissue[1]. Furthermore, studies demonstrated a drug-induced increase in glycosaminoglycans[1] and collagen[24] production along with the proliferation of gingival fibroblasts[25]. These changes are mainly mediated by inflammatory cytokines that are a part of an inflammatory response to drugs[23]. Inflammatory infiltrates found in the gingiva mainly consist of plasma cells[26]. Periodontal status is a significant predictor of DIGO, as bacterial plaque induces inflammation. A significant correlation was found between bacterial plaque and a higher risk for DIGO in patients treated with CCBs or cyclosporin[1,15,27]. In gingival tissue of patients with CCBs-associated DIGO, higher expression of androgen receptors accompanied with higher levels of type I collagen were detected, implying androgens' role in its pathogenesis[28].

DIGO-INDUCING DRUGS

The first CCB-DIGO cases date from the early 80-ties, primarily associated with nifedipine[29] and later with the use of other CCBs such as verapamil, diltiazem, amlodipine, and felodipine[30]. Early studies demonstrated the highest prevalence in patients on nifedipine (6.3%), which remains to date the leading cause of DIGO in this drug group. Other CCBs, such as amlodipine (1.7%) and diltiazem (2.2%), have a lower potential to cause DIGO[31]. The various prevalence of DIGO among different CCBs may be a consequence of pharmacokinetic characteristics, as nifedipine is more lipophilic, so it passes through cell membranes more quickly and has a half-life which allows it to reach peak levels in the plasma needed for the initiation of gingival changes[31]. However, the prevalence of DIGO caused by CCBs varies in various studies, as for CCBs in general, it ranges between 10%-20%[32]. It amounts from 15% to 85%[33,34], for nifedipine, meaning that there are additional influencing factors. Male gender, drug dosage, smoking, periodontal status, previous myocardial infarction, and concomitant use of diuretics or antiepileptic drugs increase the risk of developing DIGO in CCBs users[12,31,35]. However, drug dosage depends mostly on pharmacokinetics and pharmacodynamics and is thought to be an unreliable predictor[36]. The majority of cases develop in the first six months of therapy, with the greatest occurrence in the first month, whereas the incidence decreases with long-term use[12]. On the other hand, the study of Hatahira *et al*[13] detected a median time to onset of 262 d, so long-term monitoring is still needed for patients who will develop the changes later. DIGO occurs less often using other antihypertensive drugs, such as angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, and beta-blockers[3,37]. Therefore, in patients at risk for developing DIGO or those who already did, switching to CCBs with better safety profiles or other antihypertensive drugs is a treatment option.

Cyclosporin and tacrolimus, from the group of calcineurin inhibitors, are the leading cause of DIGO among immunosuppressive drugs[38]. Cyclosporin was the primary immunosuppressive drug in heart-transplant patients since 1980[39]. Many

heart transplant recipients (8.3%-67%) develop gingival enlargement, most of whom are treated with cyclosporin[40]. The role of cyclosporin as an inducing drug in DIGO development is well known and recognized[41]. Gingival changes in patients treated with cyclosporine show symmetry between mandibula and maxilla and within the jaw, while incisors and canines are affected the most[15]. According to the research of Hatahira *et al*[13], 70% of gingival overgrowth is attributed to cyclosporin. On the other hand, tacrolimus is another immunosuppressant often used as an alternative to cyclosporin in primary or rescue therapy[27]. It is 100 times more potent and tends to cause some side-effects common to other immunosuppressants[27,42]. However, it less often causes gingival overgrowth, and changes are less severe than those caused by cyclosporin[27]. The prevalence of DIGO among tacrolimus treated patients is around 14%[27,43]. DIGO can be detected as soon as 1-3 mo after immunosuppressive therapy initiation, and the plateau phase is reached at 9-12 mo[44]. However, gingival changes resulting from tacrolimus use appear later compared to cyclosporin, as in various studies, no changes were observed before 90 d of treatment[38,45]. Interestingly, immunosuppressants differ from other DIGO-inducing drugs since high inflammation levels and low fibrosis mostly mediate the changes[46]. Some of the predisposing factors among cyclosporin users are male gender, gingivitis, bacterial plaque, and higher cyclosporine concentrations[15,22]. Furthermore, younger patients are more frequently affected by DIGO[15], and high rates have been reported among the group of pediatric heart-transplant patients treated with cyclosporin[39,47,48]. Younger age was also a risk factor for more severe changes in patients on tacrolimus[27]. Different therapeutic patterns and higher potential of fibroblasts to proliferate and produce collagen in a group of younger patients could be a possible explanation[15,49]. Additionally, a higher risk for DIGO in tacrolimus users was observed in patients with the worse periodontal state, those previously medicated with cyclosporin[27], and a with longer duration of tacrolimus therapy[50]. The occurrence and severity of changes also depend on the concomitant use of other medications. Simultaneous use of cyclosporin and CCBs doubles the risk for DIGO, compared to using cyclosporin alone (51.9% *vs* 25%)[22]. Furthermore, the use of CCBs in tacrolimus-treated patients results in higher severity of gingival changes[27]. These findings indicate the synergistic effect of CCBs and calcineurin inhibitors. On the contrary, azathioprine has a protective effect in patients on cyclosporin or tacrolimus and lowers the risk for DIGO[27,51]. Although tacrolimus provides a better safety profile regarding DIGO and could be a treatment option in patients with cyclosporin-induced gingival overgrowth, it is important to point out that in some cases, changes persist even after the switching of therapy, especially with concomitant use of CCBs[27].

TREATMENT OPTIONS

Management of DIGO can be conservative or surgical, with the aim to provide a satisfactory cosmetic outcome and minimize discomfort and pain[1]. Non-surgical methods are the treatment of choice, including proper oral hygiene and mechanical removal of dental plaque, together with the mandatory exclusion of the offending drug[14]. Periodontal treatment reduces inflammation and prevents the need for surgical treatment in cyclosporin-treated patients[52]. A rigorous oral hygiene regime has been recommended for patients with DIGO resulting from CCBs use[32]. Since a worse periodontal state has been associated with a higher risk for DIGO[15,27], preventive measures targeting oral health could be valuable. Reduction of drug dose or switching to that of a lower potential for side-effects should always be considered, if possible. In that case, complete improvement can be expected in 1-8 wk[53] (Figure 1).

Stopping the use of CCBs or switching to non-CCB antihypertensives provides satisfactory results, but it is not always possible, as some patients may have problems controlling their hypertension[54]. In an attempt to treat gingival overgrowth caused by cyclosporin, replacing this medication with tacrolimus or everolimus remains an option[55,56] (Figure 2).

Flutamide, an androgen receptor antagonist, inhibits gingival cells' response to nifedipine and could be used to prevent or treat nifedipine associated DIGO[28]. Non-surgical methods are often not sufficient if the drug cannot be withdrawn for other reasons[54]. Persistent DIGO requires surgical treatment, which could either involve gingivectomy or periodontal flap[57]. The use of carbon dioxide lasers is a solid choice that provides adequate postoperative hemostasis[23]. Recurrence of DIGO after surgical treatment was reported in about 40% of the patients still treated with the offending drug[58]. In conclusion, the prognosis of DIGO is good, as it can be successfully

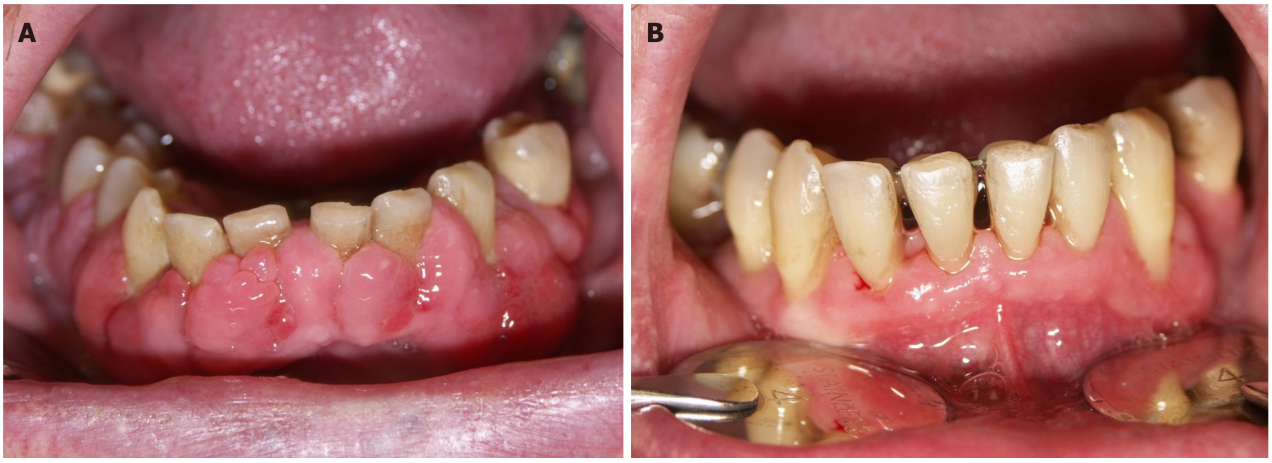

Figure 1 A complete response of a severe drug-induced gingival overgrowth case following seven weeks after amlodipine removal and six consecutive tooth scaling and cleaning treatments. A: Amlodipine induced gingival overgrowth successfully treated by vigorous weekly plaque control; B: Calculus removal during seven weeks following the drug withdrawal and substitution by angiotensin-converting enzyme inhibitor (courtesy of Prof. Vlaho Brailo).

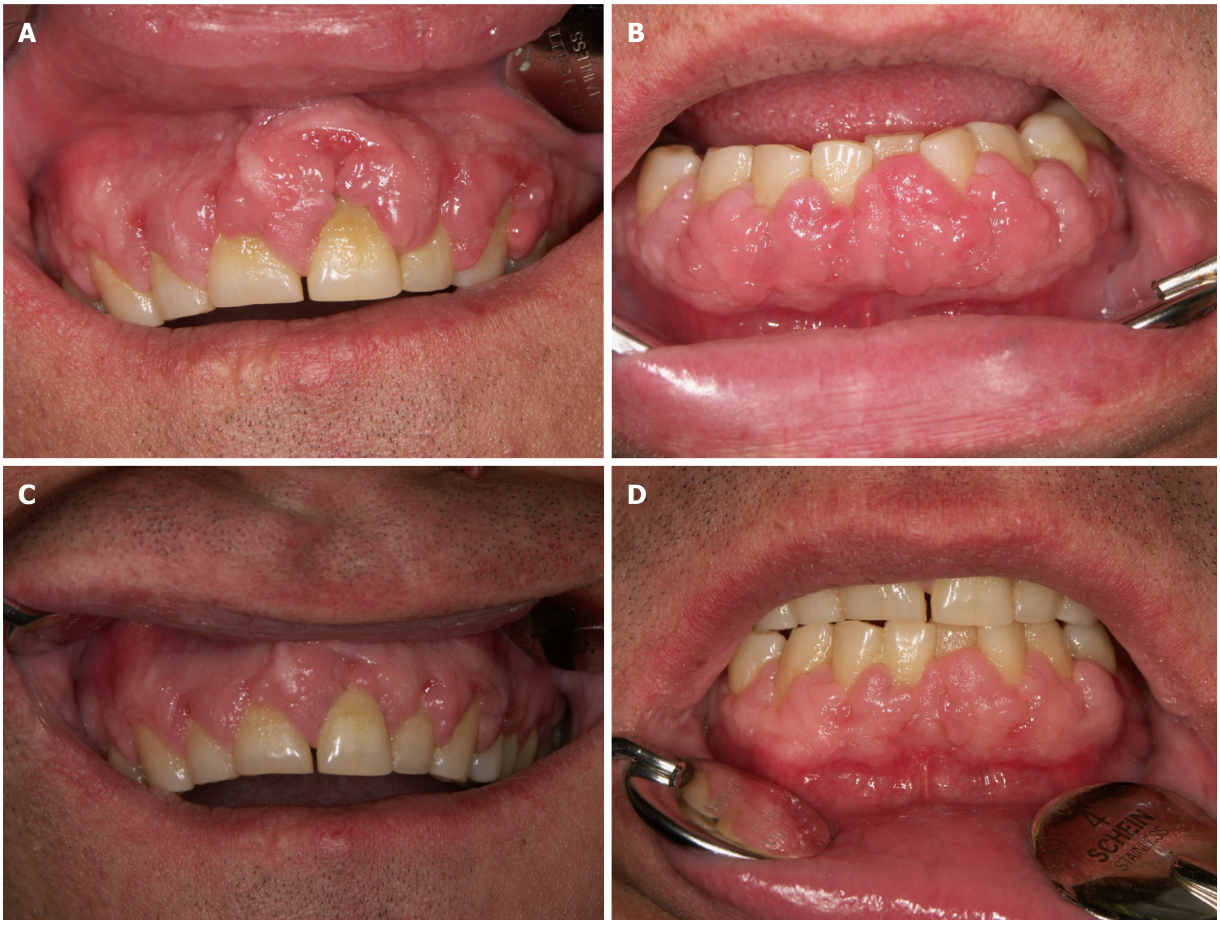

Figure 2 An improvement in a heart transplant patient, whose medication included both cyclosporin and amlodipine, four weeks following professional teeth cleaning and switching to tacrolimus and alternative antihypertensive drug. A and B: Gingival overgrowth in a heart transplant patient receiving both cyclosporin and amlodipine; C and D: An improvement is observed following conservative periodontal treatment and four weeks of switching to tacrolimus and angiotensin-converting enzyme inhibitor.

managed and resolved with discontinuation of the inducing drugs[1].

CONCLUSION

Since CCBs and immunosuppressants are widely used medications in patients with hypertension or after heart transplantation[9,10], health professionals should be aware of gingival overgrowth as an unpleasant side-effect that can result from the use of these drugs[23,55]. Although it might not be life-threatening, it poses a significant problem for the patients, not only because of the cosmetic effect but also due to the impairment of speech, eating, and maintaining oral hygiene[12,13]. Furthermore, infections resulting from the lack of proper oral hygiene could enhance the risk for cardiovascular diseases[59]. Recognizing the importance of DIGO and its effect on the patients' health is crucial for providing better health outcomes and satisfactory quality of life. If possible, treatment of choice should be changing of a drug and conservative periodontal treatment, whereas surgical treatment is reasonable only in resistant cases. Since it is multifactorial and reoccurs if the drug must be continued, efforts need to be made to find each patient's optimal treatment. An interdisciplinary approach and cooperation of medical and dental professionals are necessary to reach this goal.

REFERENCES

1 **Tungare S**, Paranjpe AG. Drug Induced Gingival Overgrowth. 2020 Oct 5. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 [PMID: 30860753]

2 **Seymour RA**, Thomason JM, Ellis JS. The pathogenesis of drug-induced gingival overgrowth. *J Clin Periodontol* 1996; **23**: 165-175 [PMID: 8707974 DOI: 10.1111/j.1600-051x.1996.tb02072.x]

3 **Ustaoğlu G**, Erdal E, Karaş Z. Influence of different anti-hypertensive drugs on gingival overgrowth: A cross-sectional study in a Turkish population. *Oral Dis* 2020 [PMID: 32991012 DOI: 10.1111/odi.13655]

4 **Kimball OP**. The treatment of epilepsy with sodium diphenyl hydantoinate. *JAMA* 1939; **112**: 1244-1245 [DOI: 10.1001/jama.1939.02800130028009]

5 **Kanade K**. Drug Induced Gingival Enlargement. Munich: GRIN Verlag, 2018: 2-10

6 **Rees TD**, Levine RA. Systematic drugs as a risk factor for periodontal disease initiation and progression. *Compendium* 1995; **16**: 20, 22, 26 passim; quiz 42 [PMID: 7758039]

7 **Marshall RI**, Bartold PM. Medication induced gingival overgrowth. *Oral Dis* 1998; **4**: 130-151 [PMID: 9680902 DOI: 10.1111/j.1601-0825.1998.tb00269.x]

8 **Lin K**, Guilhoto LMFF, Yacubian EMT. Drug-induced gingival enlargement - Part II. Antiepileptic drugs: not only phenytoin is involved. *J Epilepsy Clin Neurophysiol* 2007; **13**: 83-88 [DOI: 10.1590/S1676-26492007000200009]

9 **Asif SM**, Shaik N, Barthunia B, Kaleem SM, Zakirulla M, Kota MZ, Baig FAH. Nifedipine induced gingival enlargement in an edentulous patient: a case report with one year follow up. *BMC Oral Health* 2018; **18**: 227 [PMID: 30587167 DOI: 10.1186/s12903-018-0690-4]

10 **Kobashigawa J**, Luu M. Immunosuppression Strategies in Heart Transplantation. In: Kobashigawa J. Clinical Guide to Heart Transplantation. 1st ed. Cham: Springer, 2017: 109-135

11 **Seymour RA**, Ellis JS, Thomason JM. Risk factors for drug-induced gingival overgrowth. *J Clin Periodontol* 2000; **27**: 217-223 [PMID: 10783833 DOI: 10.1034/j.1600-051x.2000.027004217.x]

12 **Kaur G**, Verhamme KM, Dieleman JP, Vanrolleghem A, van Soest EM, Stricker BH, Sturkenboom MC. Association between calcium channel blockers and gingival hyperplasia. *J Clin Periodontol* 2010; **37**: 625-630 [PMID: 20642630 DOI: 10.1111/j.1600-051X.2010.01574.x]

13 **Hatahira H**, Abe J, Hane Y, Matsui T, Sasaoka S, Motooka Y, Hasegawa S, Fukuda A, Naganuma M, Ohmori T, Kinosada Y, Nakamura M. Drug-induced gingival hyperplasia: a retrospective study using spontaneous reporting system databases. *J Pharm Health Care Sci* 2017; **3**: 19 [PMID: 28729910 DOI: 10.1186/s40780-017-0088-5]

14 **Livada R**, Shiloah J. Calcium channel blocker-induced gingival enlargement. *J Hum Hypertens* 2014; **28**: 10-14 [PMID: 23739159 DOI: 10.1038/jhh.2013.47]

15 **Somacarrera ML**, Hernández G, Acero J, Moskow BS. Factors related to the incidence and severity of cyclosporin-induced gingival overgrowth in transplant patients. A longitudinal study. *J Periodontol* 1994; **65**: 671-675 [PMID: 7608843 DOI: 10.1902/jop.1994.65.7.671]

16 **Sabarudin MA**, Taib H. Drug-influenced Gingival Enlargement: Overview of the Clinical Features and Assessment Methods. *J Dentists* 2019; **7**: 1-7 [DOI: 10.12974/2311-8695.2019.07.1]

17 **Hasturk H**, Kantarci A. Activation and resolution of periodontal inflammation and its systemic impact. *Periodontol 2000* 2015; **69**: 255-273 [PMID: 26252412 DOI: 10.1111/prd.12105]

18 **Liccardo D**, Cannavo A, Spagnuolo G, Ferrara N, Cittadini A, Rengo C, Rengo G. Periodontal Disease: A Risk Factor for Diabetes and Cardiovascular Disease. *Int J Mol Sci* 2019; **20** [PMID: 30897827 DOI: 10.3390/ijms20061414]

19 **Radomski MW**, Palmer RM, Moncada S. Comparative pharmacology of endothelium-derived relaxing factor, nitric oxide and prostacyclin in platelets. *Br J Pharmacol* 1987; **92**: 181-187 [PMID: 3311265 DOI: 10.1111/j.1476-5381.1987.tb11310.x]

20 **Rapone B**, Ferrara E, Santacroce L, Cesarano F, Arazzi M, Liberato LD, Scacco S, Grassi R, Grassi

FR, Gnoni A, Nardi GM. Periodontal Microbiological Status Influences the Occurrence of Cyclosporine-A and Tacrolimus-Induced Gingival Overgrowth. *Antibiotics (Basel)* 2019; **8** [PMID: 31438651 DOI: 10.3390/antibiotics8030124]

21 **Meisel P**, Giebel J, Kunert-Keil C, Dazert P, Kroemer HK, Kocher T. MDR1 gene polymorphisms and risk of gingival hyperplasia induced by calcium antagonists. *Clin Pharmacol Ther* 2006; **79**: 62-71 [PMID: 16413242 DOI: 10.1016/j.clpt.2005.09.008]

22 **Thomason JM**, Seymour RA, Ellis JS, Kelly PJ, Parry G, Dark J, Wilkinson R, Ilde JR. Determinants of gingival overgrowth severity in organ transplant patients. An examination of the rôle of HLA phenotype. *J Clin Periodontol* 1996; **23**: 628-634 [PMID: 8841894 DOI: 10.1111/j.1600-051x.1996.tb00586.x]

23 **Dongari-Bagtzoglou A**; Research, Science and Therapy Committee, American Academy of Periodontology. Drug-associated gingival enlargement. *J Periodontol* 2004; **75**: 1424-1431 [PMID: 15562922 DOI: 10.1902/jop.2004.75.10.1424]

24 **Duncan MR**, Berman B. Stimulation of collagen and glycosaminoglycan production in cultured human adult dermal fibroblasts by recombinant human interleukin 6. *J Invest Dermatol* 1991; **97**: 686-692 [PMID: 1940439 DOI: 10.1111/1523-1747.ep12483971]

25 **Goriuc A**, Foia LG, Minea B, Luchian AI, Surdu AE, Toma V, Costuleanu M, Mârțu I. Drug-induced gingival hyperplasia - experimental model. *Rom J Morphol Embryol* 2017; **58**: 1371-1376 [PMID: 29556630]

26 **Deliliers GL**, Santoro F, Polli N, Bruno E, Fumagalli L, Risciotti E. Light and electron microscopic study of cyclosporin A-induced gingival hyperplasia. *J Periodontol* 1986; **57**: 771-775 [PMID: 3467061 DOI: 10.1902/jop.1986.57.12.771]

27 **Ellis JS**, Seymour RA, Taylor JJ, Thomason JM. Prevalence of gingival overgrowth in transplant patients immunosuppressed with tacrolimus. *J Clin Periodontol* 2004; **31**: 126-131 [PMID: 15016038 DOI: 10.1111/j.0303-6979.2004.00459.x]

28 **Lu HK**, Tseng CC, Lee YH, Li CL, Wang LF. Flutamide inhibits nifedipine- and interleukin-1 beta-induced collagen overproduction in gingival fibroblasts. *J Periodontal Res* 2010; **45**: 451-457 [PMID: 20337887 DOI: 10.1111/j.1600-0765.2009.01255.x]

29 **Lederman D**, Lumerman H, Reuben S, Freedman PD. Gingival hyperplasia associated with nifedipine therapy. Report of a case. *Oral Surg Oral Med Oral Pathol* 1984; **57**: 620-622 [PMID: 6588343 DOI: 10.1016/0030-4220(84)90283-4]

30 **Marshall RI**, Bartold PM. A clinical review of drug-induced gingival overgrowths. *Aust Dent J* 1999; **44**: 219-232 [PMID: 10687229 DOI: 10.1111/j.1834-7819.1999.tb00224.x]

31 **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. *J Periodontol* 1999; **70**: 63-67 [PMID: 10052772 DOI: 10.1902/jop.1999.70.1.63]

32 **Meisel P**, Schwahn C, John U, Kroemer HK, Kocher T. Calcium antagonists and deep gingival pockets in the population-based SHIP study. *Br J Clin Pharmacol* 2005; **60**: 552-559 [PMID: 16236046 DOI: 10.1111/j.1365-2125.2005.02485.x]

33 **Barak S**, Engelberg IS, Hiss J. Gingival hyperplasia caused by nifedipine. Histopathologic findings. *J Periodontol* 1987; **58**: 639-642 [PMID: 3477631 DOI: 10.1902/jop.1987.58.9.639]

34 **Fattore L**, Stablein M, Bredfeldt G, Semla T, Moran M, Doherty-Greenberg JM. Gingival hyperplasia: a side effect of nifedipine and diltiazem. *Spec Care Dentist* 1991; **11**: 107-109 [PMID: 1887359 DOI: 10.1111/j.1754-4505.1991.tb00828.x]

35 **Nery EB**, Edson RG, Lee KK, Pruthi VK, Watson J. Prevalence of nifedipine-induced gingival hyperplasia. *J Periodontol* 1995; **66**: 572-578 [PMID: 7562349 DOI: 10.1902/jop.1995.66.7.572]

36 **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 J Stomato* 2014; **4**: 169-173 [DOI: 10.4236/ojst.2014.44025]

37 **Pradhan S**, Mishra P. Gingival enlargement in antihypertensive medication. *JNMA J Nepal Med Assoc* 2009; **48**: 149-152 [PMID: 20387357]

38 **Sekiguchi RT**, Paixão CG, Saraiva L, Romito GA, Pannuti CM, Lotufo RF. Incidence of tacrolimus-induced gingival overgrowth in the absence of calcium channel blockers: a short-term study. *J Clin Periodontol* 2007; **34**: 545-550 [PMID: 17433046 DOI: 10.1111/j.1600-051X.2007.01074.x]

39 **Minami K**, von Knyphausen E, Niino T, Blanz U, Tenderich G, Wlost S, Meyer H, Körfer R. Long-term results of pediatric heart transplantation. *Ann Thorac Cardiovasc Surg* 2005; **11**: 386-390 [PMID: 16401987]

40 **Gruter MO**, Brand HS. Oral health complications after a heart transplant: a review. *Br Dent J* 2020; **228**: 177-182 [PMID: 32060460 DOI: 10.1038/s41415-020-1244-0]

41 **Montebugnoli L**, Bernardi F, Magelli C. Cyclosporin-A-induced gingival overgrowth in heart transplant patients. A cross-sectional study. *J Clin Periodontol* 1996; **23**: 868-872 [PMID: 8891939 DOI: 10.1111/j.1600-051x.1996.tb00625.x]

42 **Jacobson P**, Uberti J, Davis W, Ratanatharathorn V. Tacrolimus: a new agent for the prevention of graft-versus-host disease in hematopoietic stem cell transplantation. *Bone Marrow Transplant* 1998; **22**: 217-225 [PMID: 9720734 DOI: 10.1038/sj.bmt.1701331]

43 **Greenberg KV**, Armitage GC, Shiboski CH. Gingival enlargement among renal transplant recipients in the era of new-generation immunosuppressants. *J Periodontol* 2008; **79**: 453-460 [PMID: 18315427 DOI: 10.1902/jop.2008.070434]

44 **Lauritano D**, Moreo G, Limongelli L, Palmieri A, Carinci F. Drug-Induced Gingival Overgrowth: The Effect of Cyclosporin A and Mycophenolate Mophetil on Human Gingival Fibroblasts. *Biomedicines* 2020; **8** [PMID: 32708980 DOI: 10.3390/biomedicines8070221]

45 **Paixão CG**, Sekiguchi RT, Saraiva L, Pannuti CM, Silva HT, Medina-Pestana J, Romito GA. Gingival overgrowth among patients medicated with cyclosporin A and tacrolimus undergoing renal transplantation: a prospective study. *J Periodontol* 2011; **82**: 251-258 [PMID: 20722530 DOI: 10.1902/jop.2010.100368]

46 **Trackman PC**, Kantarci A. Molecular and clinical aspects of drug-induced gingival overgrowth. *J Dent Res* 2015; **94**: 540-546 [PMID: 25680368 DOI: 10.1177/0022034515571265]

47 **Lowry LY**, Welbury RR, Seymour RA, Waterhouse PJ, Hamilton JR. Gingival overgrowth in paediatric cardiac transplant patients: a study of 19 patients aged between 2 and 16 years. *Int J Paediatr Dent* 1995; **5**: 217-222 [PMID: 8957834 DOI: 10.1111/j.1365-263x.1995.tb00182.x]

48 **Ansari F**, Ferring V, Schulz-Weidner N, Wetzel WE. Concomitant oral findings in children after cardiac transplant. *Pediatr Transplant* 2006; **10**: 215-219 [PMID: 16573610 DOI: 10.1111/j.1399-3046.2005.00429.x]

49 **Daley TD**, Wysocki GP, Day C. Clinical and pharmacologic correlations in cyclosporine-induced gingival hyperplasia. *Oral Surg Oral Med Oral Pathol* 1986; **62**: 417-421 [PMID: 3464914 DOI: 10.1016/0030-4220(86)90291-4]

50 **Pamuk F**, Cetinkaya BO, Gulbahar MY, Gacar A, Keles GC, Erisgin Z, Arik N. Effects of tacrolimus and nifedipine, alone or in combination, on gingival tissues. *J Periodontol* 2013; **84**: 1673-1682 [PMID: 23289868 DOI: 10.1902/jop.2013.120545]

51 **Wilson RF**, Morel A, Smith D, Koffman CG, Ogg CS, Rigden SP, Ashley FP. Contribution of individual drugs to gingival overgrowth in adult and juvenile renal transplant patients treated with multiple therapy. *J Clin Periodontol* 1998; **25**: 457-464 [PMID: 9667479 DOI: 10.1111/j.1600-051x.1998.tb02474.x]

52 **Aimetti M**, Romano F, Debernardi C. Effectiveness of periodontal therapy on the severity of cyclosporin A-induced gingival overgrowth. *J Clin Periodontol* 2005; **32**: 846-850 [PMID: 15998267 DOI: 10.1111/j.1600-051X.2005.00774.x]

53 **Wynn RL**. Calcium channel blockers and gingival hyperplasia. *Gen Dent* 1991; **39**: 240-243 [PMID: 1916193]

54 **Fardal Ø**, Lygre H. Management of periodontal disease in patients using calcium channel blockers - gingival overgrowth, prescribed medications, treatment responses and added treatment costs. *J Clin Periodontol* 2015; **42**: 640-646 [PMID: 26076712 DOI: 10.1111/jcpe.12426]

55 **Penninga L**, Møller CH, Gustafsson F, Steinbrüchel DA, Gluud C. Tacrolimus *vs* cyclosporine as primary immunosuppression after heart transplantation: systematic review with meta-analyses and trial sequential analyses of randomised trials. *Eur J Clin Pharmacol* 2010; **66**: 1177-1187 [PMID: 20882273 DOI: 10.1007/s00228-010-0902-6]

56 **Stypmann J**, Engelen MA, Eckernkemper S, Amler S, Gunia S, Sindermann JR, Rothenburger M, Rukosujew A, Drees G, Welp HA. Calcineurin inhibitor-free immunosuppression using everolimus (Certican) after heart transplantation: 2 years' follow-up from the University Hospital Münster. *Transplant Proc* 2011; **43**: 1847-1852 [PMID: 21693288 DOI: 10.1016/j.transproceed.2010.12.062]

57 **Camargo PM**, Melnick PR, Pirih FQ, Lagos R, Takei HH. Treatment of drug-induced gingival enlargement: aesthetic and functional considerations. *Periodontol 2000* 2001; **27**: 131-138 [PMID: 11551304 DOI: 10.1034/j.1600-0757.2001.027001131.x]

58 **Ilgenli T**, Atilla G, Baylas H. Effectiveness of periodontal therapy in patients with drug-induced gingival overgrowth. Long-term results. *J Periodontol* 1999; **70**: 967-972 [PMID: 10505798 DOI: 10.1902/jop.1999.70.9.967]

59 **Scannapieco FA**, Bush RB, Paju S. Associations between periodontal disease and risk for atherosclerosis, cardiovascular disease, and stroke. A systematic review. *Ann Periodontol* 2003; **8**: 38-53 [PMID: 14971247 DOI: 10.1902/annals.2003.8.1.38]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com