

Primljen/ Received on 2.7.2011.  
 Revidiran/ Revised on 30.8.2011.  
 Prihvaćen/ Accepted on 19.9.2011

PRIKAZ SLUČAJA  
 CASE REPORT

doi: 10.5937/asn1164104P

## GINGIVALNO UVEĆANJE IZAZVANO NIFEDIPINOM -Gingiva i lekovi-

## GINGIVAL OVERGROWTH INDUCED BY NIFEDIPINE - Gingiva and drugs-

Ana S. Pejčić<sup>1</sup>, Ljiljana G. Kesić<sup>1</sup>, Vesna D. Živković<sup>2</sup>, Radmila R. Obradović<sup>1</sup>,  
 Milica S. Petrović<sup>1</sup>, Dimitrije S. Mirković<sup>3</sup>

<sup>1</sup> UNIVERZITET U NIŠU, MEDICINSKI FAKULTET NIŠ, KLINIKA ZA STOMATOLOGIJU, ODELJENJE ZA PARODONTOLOGIJU I ORALNU MEDICINU; <sup>2</sup> UNIVERZITET U NIŠU, MEDICINSKI FAKULTET NIŠ, INSTITUT ZA PATOLOGIJU;

<sup>3</sup> KLINIKA ZA STOMATOLOGIJU, NIŠ, SRBIJA

<sup>1</sup> UNIVERSITY OF NIŠ, FACULTY OF MEDICINE, DEPARTMENT OF PERIODONTOLOGY AND ORAL MEDICINE;

<sup>2</sup> UNIVERSITY OF NIŠ, FACULTY OF MEDICINE, INSTITUTE OF PATHOLOGY; <sup>3</sup> CLINIC OF DENTISTRY, NIŠ, SERBIA

### Apstrakt

**Uvod.** Gingivalno uvećanje izazvano difenilhidantoinom (Dilantin) dosta je opisivano u literaturi. Odnedavno, pojavili su se i drugi lekovi koji dovode do uvećanja gingive kao i Dilantin.

**Čilj.** Nifedipin, kalcijum-blokator, koristi se u terapiji kardiovaskularnih oboljenja zbog njegovog inhibitornog delovanja na jone kalcijuma koji dolaze do mišićnih ćelija srca i krvnih sudova. U nekim slučajevima uzimanja ovog leka, kao sporedni efekat, može se javiti i prekomerni rast gingivalnog tkiva. Ovim člankom je prikazan jedan slučaj uvećanja gingive uzimanjem nifedipina.

**Diskusija.** U literaturi postoje podaci koji govore o sličnostima u promenama koje izazivaju difenilhidantoin i nifedipin. U radu je prezentovana diskusija o kliničkim i histološkim promenama kao i o mogućoj patogenezi poremećaja. Iako se još uvek ne zna tačan mehanizam nastanka hiperplazije gingive, potvrđeno je da sa prekidom uzimanja nifedipina, dolazi do regresije hiperplastične gingive.

**Zaključak.** Može se zaključiti da se uvećanje gingive javlja kod pacijenata koji u terapiji koriste nifedipin, ali samo na mestima gde su prisutni lokalni faktori zapaljenja.

**Ključne reči:** gingiva, lekovi, gingivalno uvećanje

### Abstract

**Introduction.** Gingival overgrowth induced by diphenylhydantoin (Dilantin) has been well documented in the literature. Recently, there have been other medications with side effects causing Dilantin-like gingival overgrowth.

**Aim.** Nifedipine, the calcium-blocker, is used in the treatment of cardiovascular diseases due to its inhibitory effect on calcium ions that reach the heart muscle cells and blood vessels. In some cases, the gingival bissue overgrowth can occur as a side effect of the drug. This article presents a case in which nifedipine, a calcium-channel blocker, induced gingival overgrowth.

**Discussion.** In the literature there are data that show the similarities in the changes cause by difenilhidantoin and nifedipine. A discussion on the clinical and histological features and possible pathogenesis of the disorder is presented. Although the exact mechanism of gingival hyperplasia is not yet known, it has been confirmed that with an interruption of taking nifedipine, there was regression of hyperplastic gingiva.

**Conclusion.** It can be concluded that gingival overgrowth occurs in patients with nifedipine therapy only in the area where local inflammatory factors are present.

**Key words:** gingiva, drugs, gingival enlargement

### Uvod

U literaturi je 1939. godine prvi put zabeleženo da je difenilhidantoin (Dilantin) uzrok gingivalnog uvećanja<sup>1</sup>. Od tada je upotreba i drugih lekova, kao što su ciklosporini - imunosupresivi<sup>2</sup>, natrijum valproat - lek za epilepsiju<sup>3</sup> i nifedipin - kalcijum-blokator, koji

### Introduction

In 1939 diphenylhydantoin (Dilantin) was first reported to cause gingival overgrowth<sup>1</sup>. Since then, other medications have been associated with gingival overgrowth, such as cyclosporine, an immunosuppressive agent<sup>2</sup>, sodium valproate, an anti-epileptic agent<sup>3</sup>, and nifedip-

### Address for correspondence:

Ana Pejčić DDS, MSD, PhD  
 Nade Tomic 3/5  
 18000 Nis  
 Serbia  
 Phone: +381(0)642572178  
 E-mail: drana Pejčić@hotmail.com

© 2011 Faculty of Medicine in Nis. Clinic of Dentistry in Nis. All rights reserved / © 2011 Medicinski fakultet Niš. Klinika za stomatologiju Niš. Sva prava zadržana

se koristi u lečenju angine pectoris, povezivana sa uvećanjem gingive. Stanje je, klinički i histološki, ličilo na gingivalna uvećanja izazvana drugim lekovima<sup>4,5</sup>. Nifedipin je relativno nov lek koji se sve više koristi za lečenje svih vrsta angine pectoris i arterijske hipertenzije<sup>6</sup>. Glavna uloga nifedipina je da inhibira priliv ekstracelularnih jona kalcijuma kroz membranu glatkih mišićnih ćelija srca i krvnih sudova, bez menjanja koncentracije kalcijuma u serumu. Jedan od sporednih efekata ovog leka je prekomerni rast gingivalnog tkiva, koji je prvi put opisao Lederman 1984. godine<sup>7</sup>.

Ovaj članak predstavlja prikaz slučaja koji dokazuje da primena nifedipina dovodi do uvećanja gingive.

### **Prikaz slučaja**

Kod 48-godišnjeg muškarca konstatovan je višak tkiva gingive oko zuba. On je došao na Odeljenje za parodontologiju Stomatološke klinike u Nišu radi pregleda gingive, koja se, prema pacijentovim rečima, postepeno



*Sl.1. Klinički prikaz gingivalne hiperplazije*  
*Fig. 1. Clinical presentation of gingival hyperplasia.*

povećavala. Od strane kliničara konstatovano je da su bila prisutna polja uvećane gingive, naročito u prednjem području mandibule (Sl.1). Pacijent nije imao nikakve profesionalne stomatološke preglede od kad je imao infarkt miokarda pre četiri godine. Pacijent je naveo da uzima veliki broj lekova za lečenje angine pectoris i hipertenzije. Jedan od lekova koji uzima je i nifedipin, i to 90 mg četiri puta dnevno. Pacijent je ove lekove uzimao oko 1 ½ do 2 godine.

Tkivo je klinički bilo egzofitično, nepravilnih površina. Prilikom pregleda uočeno je da je uglavnom labijalna gingiva prednjih donjih

ine, a calcium-channel blocker used in the treatment of angina pectoris. Both clinically and histologically, the condition resembled other cases of drug-induced gingival overgrowth<sup>4,5</sup>. Nifedipine is a relatively new and increasingly used medication for treatment of all kinds of angina pectoris and arterial hypertension<sup>6</sup>. The principal action of nifedipine is to inhibit the influx of extracellular calcium ions across the membranes of cardiac and vascular smooth muscle cells, without changing serum calcium concentration. One of the side effects of this drug is gingival overgrowth which was first described in 1984 by Lederman<sup>7</sup>. This article presents a case with evidence for nifedipine-induced gingival overgrowth.

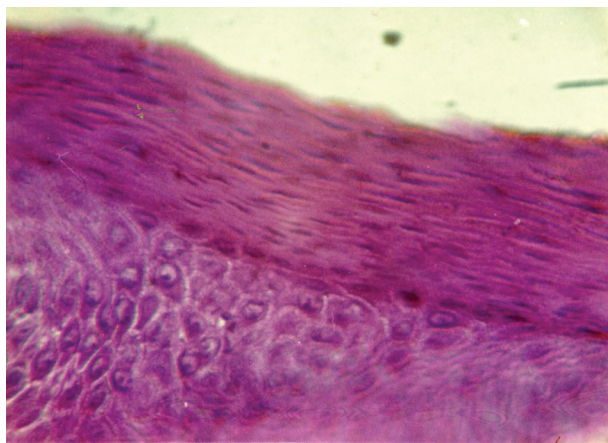
### **Case report**

A 48-year-old man was noted to have an excess of gingival tissue around the teeth. He came to the Department of Periodontology Clinic of Dentistry Niš for an overview of the gingiva, which, according to the patient's words, gradually enlarged. It was noted by the clinician that areas of gingival enlargements were present, especially in the mandibular anterior area (Fig.1). The patient had received no professional dental care since he had a myocardial infarction four years before. The patient said that he took a large number of drugs for the treatment of angina pectoris and hypertension. One of these medication included nifedipine, 90mg four times daily. The patient was taking these medication for approximately 1½ to 2 years.

The clinical appearance of the tissue was exophytic with an irregular surface. We noted that the labial gingivae of the anterior mandibular teeth were most frequently involved, which was in keeping with the results obtained in other studies<sup>8,9</sup>. The hyperplastic tissue was red, smooth and shiny, with no pain on touch, and bled easily on probing. Gingival tissue around the crown reached the occlusal tooth surface, with periodontal pockets measuring 5mm, plaque and calculus. The patient said that this area was difficult to clean. The dental treatment included scaling and root planning and instructions on appropriate method for brushing teeth<sup>10</sup>. The hyperplastic tissues were removed surgically by gingivectomy to reduce gingival pockets and to produce an approximal area which was easier for the patient to keep clear<sup>11</sup>. The tissue was subsequently removed and examined histologically. Commercially available

zuba bila zahvaćena, što se poklapa sa pacijentima iz drugih studija<sup>8,9</sup>. Hiperplastično tkivo bilo je crveno, glatko i sjajno, bez bola na dodir, i lako je krvarilo na blagu provokaciju. Gingivalno tkivo oko krunice dosezalo je okluzalne površine zuba, sa pseudodžepovima od 5 mm, plakom i kamencem. Pacijentima je bilo teško da čiste ova mesta.

Dentalni tretman uključivao je uklanjanje kamenca, konkremenata i kiretažu mekog tkiva sa instrukcijama o odgovarajućoj tehnici pranja zuba<sup>10</sup>. Hiperplastično tkivo je zatim uklonjeno hirurški gingivektomijom, da bi se smanjili gingivalni džepovi i napravila područja laka za održavanje<sup>11</sup>. Uklonjeno tkivo je histološki ispitano. Komercijalno dostupan rastvor hlorheksidina (0.12%) korišćen je radi sprečavanja akumulacije oralnog biofilma i razvoja upale gingive.



Sl. 2. Parakeratoza  
Fig. 2. Parakeratosis

### Histološki nalazi

Gingivalno tkivo, uzeto tokom gingivektomije, obrađeno je na Institutu za patologiju, Medicinskog fakulteta Univerziteta u Nišu. Tkivo je fiksirano u 10% rastvoru formalina, zatim je bojeno hematoksilinom i eozinom, i na kraju posmatrano pod svetlosnim mikroskopom.

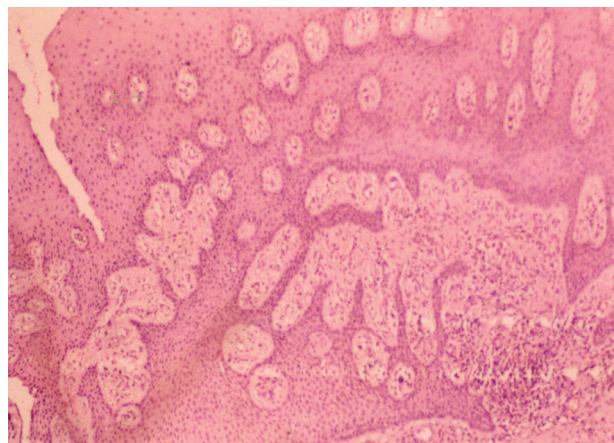
Histološki pregled pokazao je epitelnu hiperplaziju sa akantozom epitela i parakeratozom (Sl. 2). Videla se i pseudoepiteliomatозна hiperplazija (Sl. 3) i izduženje rete-pegusa, koji su često povezani (Sl. 4). Vezivno tkivo pokazalo je velike snopove gustih kolagenih vlakana

chlorhexidine rinse (0.12%) was used to help control plaque accumulation and to reduce the development of gingival inflammation.

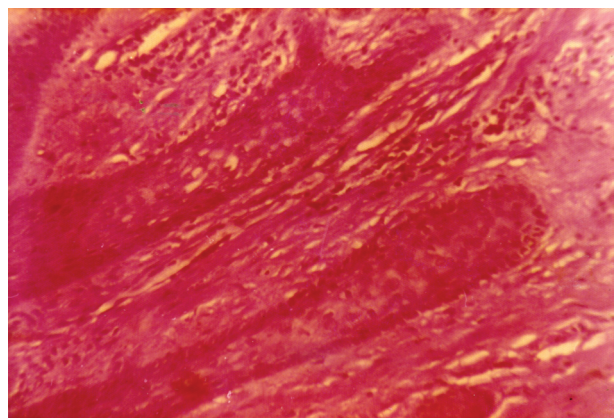
### Histological findings

The gingival tissue taken during gingivectomy was processed at the Institute of Pathology, University of Nis, Faculty of Medicine. The tissue was fixed in 10% formalin saline, stained with haematoxylin and eosin, then viewed using light microscopy.

Histological examination showed epithelial hyperplasia with acanthosis of the overlying epithelium and parakeratosis (Fig. 2). There was pseudoepitheliomatous hyperplasia as well (Fig. 3) and elongations of rete pegs, which anastomosed frequently (Fig. 4). The connective tissue showed large bundles of dense collagenous fibers with a moderate increase in fibroblasts. In addition, there was an inflammatory reac-



Sl. 3. Pseudoepiteliomatозна hiperplazija  
Fig. 3. Pseudoepitheliomatous hyperplasia



Sl. 4. Produženje rete-pegusa i invaginacija epitela u vezivno tkivo

Fig. 4. The elongations of rete-pegs and epithelium invaginating the underlying connective tissue

sa umerenim urastanjem u fibroblaste. Dodatno je postojala i inflamatorna reakcija, koja se uglavnom sastojala od plazma ćelija lokalizovanih perivaskularno. Krvni sudovi bili su prošireni. Ovaj prikazan slučaj uvećanja gingive povezan je sa upotrebom nifedipina<sup>12</sup>. Ovo stanje je, klinički i histološki, bilo veoma slično slučaju posmatranom nakon primene Dilantin-a<sup>1</sup>.

## Diskusija

Nifedipin spada u grupu lekova pod nazivom kalcijum-blokatori. Drugi lekovi iz ove grupe su verapamil i diltiazem. Ovi lekovi deluju kao antikalcijum lekovi i umanjuju kontrakcije miokarda i kontrakcije glatkih mišića koronarnih arterija indukovane kalcijumom.

Prikazani slučaj pokazuje velike sličnosti sa uvećanjem gingive difenilhidantoinom.

Histološke sličnosti između ovog slučaja i drugih slučajeva uvećanja gingive izazvanih Diltiazemom i difenilhidantoinom su očigledne<sup>13,14</sup>. U svim ovim slučajevima uvećanja gingive, epitelna hiperplazija sa dugim, vitkim rete-pegs-ima i umerenim ili velikim uvećanjem kolagenih snopova, uočeni su mikroskopskim pregledom. U većini slučajeva, došlo je i do povećanja inflamacije uz prisustvo limfocita, plazma ćelija i leukocita<sup>14</sup>. Hiperplazija je najčešće povezana sa inflamatornom reakcijom, što ukazuje na potrebu rigoroznih mera higijene koje usporavaju njen napredak i umanjuju njeno trajanje.

Tačan mehanizam delovanja nifedipina u izazivanju uvećanja gingive je nepoznat u ovom trenutku. Takođe, nema odgovora na pitanje zašto se uvećanje gingive ne pojavljuje kod svih pacijenata lečenih nifedipinom, već samo kod pojedinih.

Različite studije su pokušale da definišu mehanizam uvećanja gingive<sup>15,16</sup>. Hassell je sa svojim saradnicima<sup>17</sup> pokazao da fibroblasti, izdvojeni iz hiperplastičnog gingivalnog tkiva pacijenata koji uzimaju fenitron, proizvode veću količinu ekstracelularne neaktivne kolagenaze, sugerirajući da hiperplazija rezultira delimično i od umanjene degradacije kolagena.

Dva glavna puta, inflamatorni i neinflamatorni, već su predloženi. Neinflamatorni mehanizmi obuhvataju neispravne aktivnosti kolagenaze zbog smanjenja unosa folne kiseline<sup>18</sup> i regulaciju keratinocitnog faktora rasta<sup>15</sup>. S

tion mainly composed of plasma cells located perivascularly. The blood vessels were dilated. This case of gingival overgrowth was associated with the use of nifedipine<sup>12</sup>. Both clinically and histologically, this condition was very similar to that observed after administration of Dilantin<sup>1</sup>.

## Discussion

Nifedipine is part of a group of drugs called calcium-channel blockers. Other drugs in this group are verapamil and diltiazem. These drugs act as anticalcium agents and suppress myocardial contraction and calcium induced contraction of the smooth muscles of the coronary arteries.

The reported case shows strong similarities to diphenylhydantoin gingival overgrowth. The histological similarities between our case and those reported cases of Diltiazem and diphenylhydantoin induced gingival overgrowth are obvious<sup>13</sup>. In all these cases, gingival overgrowth, epithelial hyperplasia with long, slender rete pegs and a moderate to large increase in collagen bundles, can be seen on microscopic examination. In most cases, there was an increase in inflammation with the presence of lymphocytes, plasma cells, and leukocytes<sup>14</sup>.

The hyperplasia is most often associated with an inflammatory reaction, suggesting that rigorous hygiene measures may retard its progress and diminish its extent.

The exact mechanism of nifedipine action in causing gingival enlargement is unknown at present. There is also no answer to the question why gingival enlargement appears in some patients treated with nifedipine, and not in all of them.

Various studies have attempted to define the mechanism of gingival enlargement<sup>15,16</sup>. Hassell with his colleagues<sup>17</sup> showed that fibroblast derived from hyperplastic gingival tissue of patients taking phenytion produced an increased amount of extracellular inactive collagenase, suggesting the hyperplasia resulted, in part, from diminished collagen degradation.

Two main inflammatory and non-inflammatory pathways have already been suggested. The proposed non-inflammatory mechanisms include defective collagenase activity due to decreased uptake of folic acid<sup>18</sup> and upregula-

druge strane, upala se može razviti kao rezultat direktnog toksičnog dejstva koncentrovanog leka u gingivalnoj tečnosti i bakterijskom biofilmu<sup>19</sup>.

Klinički nalazi u ovom slučaju pokazali su da je hiperplastična promena gingive počela samo na onim mestima koja su pokazivala znakove upale, ali ne i na zdravim mestima, što je u skladu sa radom Chiu-a<sup>8</sup>.

Ova zapažanja ukazuju na to da su lokalni faktori i prisutna inflamacija od suštinskog značaja za nastanak hiperplazije gingive indukovane upotrebom nifedipina. Ovaj slučaj takođe pokazuje da nema znakova recidiva hiperplazije nakon eliminacije lokalnih inflamatornih faktora (česta kontrola oralnog biofilma i hirurški uklonjeno hiperplastično tkivo gingive), čak i kada je upotreba nifedipina nastavljena, što je u skladu sa drugim radovima<sup>20,21</sup>.

### **Zaključak**

Može se zaključiti da se uvećanje gingive javlja kod pacijenata koji u terapiji koriste nifedipin, ali samo na mestima gde su prisutni lokalni faktori zapaljenja. Sa prekidom upotrebe nifedipina, javlja se regresija hiperplazije gingive. Ovo je potvrđeno i kod ovde prikazanog pacijenta, koji je prekinuo sa upotrebom ovog leka nakon hirurške intervencije.

tion of keratinocyte growth factor<sup>15</sup>. Alternatively, inflammation may develop as a result of direct toxic effects of concentrated drug in gingival cervical fluid and bacterial biofilm<sup>19</sup>.

The clinical findings in this case showed that hyperplastic change of gingiva started only in areas displaying signs of inflammation, but not in healthy areas, which is in accord with the Chiu study<sup>8</sup>.

These observations suggest that local factors and associated inflammation are essential for the onset of the nifedipine-induced gingival hyperplasia. This case report also demonstrates that no signs of recurrence of hyperplasia were observed after the elimination of the local inflammatory factors (extensive oral biofilm control and surgical removal of the hyperplastic gingival tissue), even though the administration of nifedipine was continued which is in keeping with other studies<sup>20, 21</sup>.

### **Conclusion**

It can be concluded that gingival overgrowth occurs in patients with nifedipine therapy only in the area where local inflammatory factors are present. With discontinuation of nifedipine, there is regression of the gingival hyperplasia. This was confirmed in this patient since he discontinued with medication after surgical intervention.

## LITERATURA / REFERENCES

1. Kimball OP. The treatment of epilepsy with sodium diphenylhydantoinate. *JAMA* 1939; 112: 1244-1245.
2. Hyland PL, Traynor PS, Myrillas TT et al. The effects of cyclosporin on the collagenolytic activity of gingival fibroblasts. *J Periodontol* 2003; 74(4): 437-45.
3. Lin CJ, Yen MF, Hu OY et al. Association of galactose single-point test levels and phenytoin metabolic polymorphisms with gingival hyperplasia in patients receiving long-term phenytoin therapy. *Pharmacotherapy* 2008; 28(1): 35-41.
4. Thomason JD, Fallaw TL, Carmichael KP, Radlinsky MA, Calvert CA. Gingival hyperplasia associated with the administration of amlodipine to dogs with degenerative valvular disease (2004-2008). *J Vet Intern Med* 2009; 23(1): 39-42.
5. Triveni MG, Rudrakshi C, Mehta DS. Amlodipine-induced gingival overgrowth. *J Indian Soc Periodontol* 2009; 13: 160-163.
6. Bokor-Bratic M, Vuckovic N, Selakovic S. Gingival hyperplasia during treatment with nifedipine. *Med Pregl* 1998; 51(9-10): 445-448.
7. Lederman D, Lumerman H, Reuben S, Freedman P. Gingival hyperplasia associated with nifedipine therapy. Report of a case. *Oral Surg Oral Med Oral Pathol* 1984; 57: 620-622.
8. Chiu HC, Lan GL, Chiang CY et al. Upregulation of heme oxygenase-1 expression in gingiva after cyclosporine: a treatment. *J Periodontol* 2008; 79(11): 2200-2206.
9. Conde SA, Aarestrup FM, Vieira BJ, Bastos MG. Roxithromycin reduces cyclosporine-induced gingival hyperplasia in renal transplant patients. *Transplant Proc* 2008; 40(5): 1435-1438.
10. 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.
11. Mavrogiannis M, Ellis JS, Tomason JM, Seymour RA. The management of drug-induced gingival overgrowth. *J Clin Periodontol* 2006; 33: 434-439.
12. Brkić Z. Histopathologic investigation of nifedipine-induced gingival hyperplasia in Westar rats. *Vojnosanit Pregl* 2005; 62(3): 207-211.
13. Lafzi A, Farahani RM, Shoja MA. Phenobarbital-induced gingival hyperplasia. *J Contemp Dent Pract* 2007; 8(6): 50-56.
14. Lafzi A, Farahani RMZ, Shoja MAM. Amlodipine induced gingival hyperplasia. *Med Oral Patol Oral Cir Bucal* 2006; 11: E480-482.
15. Das SJ, Olsen I. Keratinocyte growth factor is upregulated by hyperplasia-inducing drug nifedipine. *Cytokine* 2000; 12: 1566-1569.
16. Sonmez S, Cavdar C, Gunduz C, et al. Do MMP-1 levels of gingival fibroblasts have a role in the gingival overgrowth of cyclosporine-treated patients? *Transplant Proc* 2008; 40(1): 181-183.
17. Hassell TM. Evidence for the production of an inactive collagenase by fibroblast from phenytoin enlarged human gingiva. *J Oral Pathol* 1982; 11: 310-317.
18. Xiao Li. Nifedipine Intake Increases the Risk for Periodontal Destruction in Subjects With Type 2 Diabetes Mellitus. *J Periodontol* 2008; 79(11): 2054.
19. van der Vleuten CJ, Trijebels-Smeulders MA, van der Kerkhof PC. Telangiectasia and gingival hyperplasia as side-effects of amlodipine (Norvasc) in a 3-years-Old girl. *Acta Derm Venereol* 1999; 79: 323-324.
20. Ramalho VL, Ramalho HJ, Cipullo JP, Azoubel R, Burdmann EA. Comparison of azithromycin and oral hygiene program in the treatment of cyclosporine-induced gingival hyperplasia. *Ren Fail* 2007; 29(3): 265-270.
21. Devanna R, Asif K. Interdisciplinary management of a patient with a drug-induced gingival hyperplasia. *Contemp Clin Dent* 2010; 1: 171-176.