Treatment Methods Conditioned by the Gravity of Drug-Induced Gingival Hyperplasias

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The first drug discovered to be involved in the development of gingival hyperplasia is phenytoin, which is indicated in the treatment of epileptic patients. The other drugs are calcium channel blockers with vasodilating effect. The most important one is Nifedipine, while Ciclosporin A, which is used as an immunosuppressant in the prevention of transplant rejection, causes gingival hyperplasia as a secondary effect. Gingival hyperplasia can reach an impressive volume, completely covering the dental crown and affecting the masticatory and physiognomic functions. The elucidation of the mechanism, by which drug-induced gingival hyperplasia occurs, favoring factors and the choice of conservative or surgical treatment methods, emphasizing the prophylactic treatment. The study batch was subject to intraoral and extraoral clinical examinations and the data were included in the dental treatment sheet of each patient, 11 patients aged over 60 years, who came to the Clinic ... in the period 2014-2016. The diagnosis was based on the anamnesis, the clinical aspect of the lesions and the histopathological examination. After the surgical excision of the hyperplasia affected area, recurrence was prevented by dispensarizing the patients and controlling the bacterial plaque through rigorous oral hygiene. Treatment depends on the severity of the lesions, as well as on the physionomic and masticatory functions. Conservative etiological therapy is attempted, by removing the bacterial plaque and local irritant factors, by reducing the dose of drugs, or by changing the systemic medication.

Keywords: systemic disorders, calcium channel blockers, immunosuppressants, lesion severity, functional disorders

Gingival hyperplasia is a lesion of the covering periodontium, characterized by an increase in the volume of the interdental papillae and the free gingival margin, sometimes extended to the attached gum, up to the muco-gingival boundary [1-3].

Due to the association and persistence of the bacterial plaque and the local irritants, which cause inflammation of the gum, gingival hyperplasia is aggravated by evolving towards periodontitis, with dental mobility, dental migration and even the spontaneous loss of teeth. In the absence of rigorous mouth hygiene, the lesion has a reserved prognosis[4,5] .

Other complications, such as the overinfection of lesions with gingival pain at the slightest touch, make eating and oral hygiene impossible. There are cases of lesion progression to premalignancy and even malignancy, if local irritation is chronic.

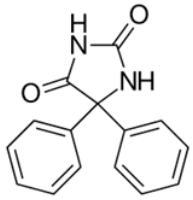
Drug-induced gingival hyperplasia is a side effect of the treatment with three large drug groups:

- Anticonvulsants (Phenytoin, Phenobarbital etc);
- immunosuppressants (Cyclosporin A);
- coronary vasodilators and calcium channel blockers (Nifedipine, Diltiazem, Amelodipine etc.).

The development of hyperplasia lesions is closely related to preexisting or coexisting gingival inflammation caused by bacterial plaque, which favors the installation and worsening of drug-induced hyperplasia lesions[6,7].

Phenytoin, was introduced into medical practice as anticonvulsant for the treatment of epileptic patients by Merrit and Puttman in 1938. Later on, in 1939, Kimball highlighted gingival hyperplasia as a side effect of phenytoin and, in 1948, Brandon demonstrated the direct action of phenytoin on gingival tissues[8,9].

Phenytoin was synthesized in 1908 by Biltz and it has the following chemical structure: 5,5-diphenyl-2,4-imidazoline monosodium salt (fig.1) Gross formula: $C_{15}H_{12}N_2O_2$



Actually, a metabolite of phenytoin is responsible for its local effects: 5- (p-hydroxyphenyl) -5-phenyl-hydantoin. Phenytoin decreases the permeability of the cell membrane and reduces the influx of calcium ions, as well as the excitability of the nervous tissue, inhibiting the propagation of nerve impulses in the brain and blocking the intracellular calcium system. In this way, it reduces or cancels the secretory functions of all the affected cells.

A structural analogy between phenytoin and folic acid has been demonstrated, suggesting that phenytoin may act as a competitive antagonist of folic acid, interfering with its metabolism in the tissue.

In 1970, Obsen and Jensen demonstratd that folic acid decreases the incidence or severity of gingival hyperplasia, by interfering with the production of 5β-hydroxyphenyl-5-phenylhydantoin (p-HFFH), the main metabolite of

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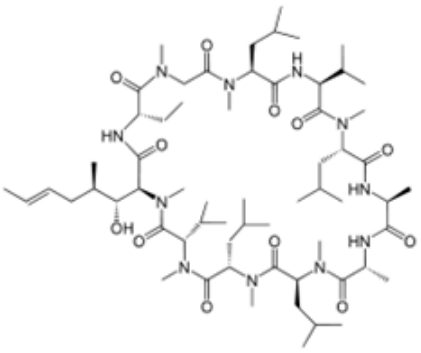
phenytoin, which is responsible for the production of gingival hyperplasias[10].

Phenytoin has a depressant effect on the immune system, exacerbating gingival inflammation during bacterial plaque aggression. The occurrence and severity of pituitary-induced gingival hyperplasia are proportional to the dose and duration of treatment. Phenytoin stimulates the proliferation of both junctional epithelium and fibroblasts, which synthesize an increased amount of procollagen, as well as sulfate components of GAG, which increases both the non-fibrillary mass of the base substance and the quantity of collagen in the corion. That inactivates collagenase, i.e. it reduces the degradation of the fibrillary component of collagen in the fundamental substance of the gingival chorion. It seems that gingival hyperplasia occurs also in the absence of bacterial plaque, tartar and other irritant factors in patients with good oral hygiene. The presence of the bacterial plaque causes an overgrowth of gingival inflammation that aggravates gingival hyperplasia[11].

The susceptibility to phenytoin-induced gingival hyperplasia depends on the existence of a stable, genetically determined sub-population of fibroblasts in the gingival tissue that respond to this substance.

Ciclosporin A is an immunosuppressant obtained from the fermentation of two fungi: Trichoderma polisporum and Cilindrocarpon lucidum.

Gross formula: $C_{62}H_{111}N_{11}O_{12}$



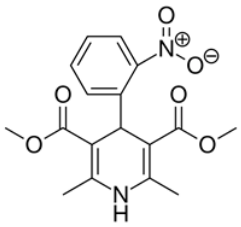
Cyclosporine:

It was discovered in 1972. It is a neutral, very lipophilic, cyclic polypeptide composed of 11 amino acids. It is not soluble in water, but is dissolved in ethanol.

The factors that could influence cyclosporin A-induced gingival hyperplasia are: Individual sensitivity to the drug itself or to some of its metabolites have certainly a role. The duration of treatment affects the installation of gingival hyperplasia and the dose of cyclosporin A seems to play a quite important role in the occurrence of associated gingival hyperplasia and the severity of the lesion. Oral hygiene is involved in the occurrence of gingival hyperplasia in patients treated with cyclosporin A, due to the presence of the inflammatory gingival component, which favors the installation of hyperplasia[12,13].

Nifedipine is the most active representative of the entire group, acting as a calcium channel blocker.

In small concentrations, it inhibits the influx of calcium ions into myocardial cells and vascular smooth muscle cells, without altering the serum concentration of calcium. Consequences: vasodilatation of the coronary arteries, strong, long-lasting, peripheral vasodilatation and decrease in peripheral resistance.



Chemical structure of Nifedipine,
Gross formula of the molecule $C_{17}H_{18}N_2O_6$

Local side effects: Gingival hyperplasia, the occurance of which is influenced by unsatisfactory oral hygiene, the presence of local irritants, the association of Ciclosporin A treatment, the dose and the duration of treatment[14].

Not all patients treated with Phenytoin, Ciclosporin A or Nifedipine develop drug-induced gingival hyperplasia. The susceptibility of individuals depends on their genetic predisposition. The drugs that induce gingival hyperplasia may alter the metabolism of human gingival fibroblasts[15].

Each of the three groups of drugs that cause drug-induced gingival hyperplasia are metabolized by members of the P450 cytochrome enzyme family, which represents a significant genetic polymorphism and leads to individual variations in enzyme activity levels[16]. The inherited variation in the metabolization of the three drug groups may influence the patient's response to treatment, in the form of gingival hyperplasia.

The inflammation produced by the bacterial plaque plays an important role in the production of gingival hyperplasia, especially in the case of Ciclosporin A or Nifedipine, but it seems to be less important in the case of phenytoin[17,18].

Once installed, gingival hyperplasia is maintained for as long as the treatment is in progress. Clinical trials have shown that the discontinuation of treatment causes the spontaneous regression of gingival hyperplasia in the absence of any periodontal treatment; but opinions are divided.

Phenytoin-induced gingival hyperplasia- The lesions begin at the level of the gingival papillae, reaching their maximum development in the first year of treatment [19].

In the absence of a secondary inflammation, the hyperplastic gum (the presence of bacterial plaque is not absolutely necessary for the occurrence of phenytoin-induced hyperplasia) presents an increased volume, pink color, granular appearance, firm and fibrous consistency and slight bleeding.

If a secondary inflammation occurs, the appearance of the hyperplasic gum changes: the hyperplasia increases in size; the gum turns red or purple; its appearance is edematous and it has a friable and depressible consistency, as well as smooth glossy surfaces. There is also spontaneous bleeding, when brushing or probing.

Young patients experience a predominance of gingival fibrosis with moderate inflammation, while in the case of older patients the inflammatory component predominant.

Gingival hyperplasia lesions rarely occur in edentulous patients.

Ciclosporin A-induced Hyperplasia- the lesions begin between the first and the third month, reaching maximum severity after one year of treatment.

The lesions are preceded by a feeling of pain and paresthesia; the interdental papillae are affected and the lesions progress towards the free gingival edge, respecting the attached gum. The localization is more frequent on the

vestibular side of the dental crown and in the front of the arcade[20,21].

The lesions present a congested appearance of the gum and bleeding is more pronounced in the case of Ciclosporin A, which shows that the gingival inflammation is more important.

The enlarged gum is bright red and glossy, with a lobulated, edematous appearance and the presence of false pockets on palpation. The radiological examination reveals the absence of bone lysis. In advanced stages, the lesions can completely cover the crown of the tooth, affecting the physiognomy, phonation and hygiene. There was no evidence of total edema.

Nifedipine-induced gingival hyperplasia- The first lesions occur in the first month of treatment and the most important changes are observed after approximately 10 months of treatment. It appears at the level of the proximal papillae and extends up to the free gingival margin, sometimes up to the attached gum. In time, the lesions generalize and the damage is more pronounced at vestibular level than orally, more in the frontal area than in the lateral one and more in the maxilla than in the mandible[22].

The volume of the hyperplasic gum depends on the administration period, the dose and the coexistence of the inflammation. The gum has a purplish red color and soft depressible consistency, with ulcerations covered by white-yellow fibrous deposits[23,24].

The hyperplasic gum is generally detachable from the crown of the tooth, revealing sloughy tissue deposits covered with purulent exudates[25,26]. At palpation, it is possible to observe the presence of subgingival tartar, false periodontal pockets and no bone lysis.

Experimental part

Material and method

The study batch was subject to intraoral and extraoral clinical examinations and the data were included in the dental treatment sheet of each patient, 11 patients aged over 60 years, who came to the Clinic in the period 2014-2016

Results and discussions

The 11 patients came due to the changes in the volume and appearance of the gum, spontaneous bleeding when brushing, and, in more advanced cases, due to the impairment of the physiological and masticatory functions. Inflammation is accentuated and the patients present sensitivity, localized pain in the affected gum, spontaneously or when brushing, which leads to inability to clean the teeth properly.

Distribution by gender: 8 women (72.72%) and 3 males (27.28%).

According to the place of origin, 6 cases (54.54%) are from rural areas, and 5 cases (45.46%), from an urban environment.

As far as the personal history is concerned, we had to identify the general complaints of the patients and the medical treatment that was followed (Phenytoin, Ciclosporin A, Nifedipine).

Table 1

DISTRIBUTION OF CASES OF DRUG - INDUCED GINGIVAL HYPERPLASIA

Drug	N° of cases	Percentage
Phenytoin	3	27.27%
Nifedipine	7	63.63%
Ciclosporin A	1	9.10%

The three hospitalized cases were undergoing *phenytoin* treatment for epilepsy seizures for about one year and a half. The chosen medication should be individualized, depending on the patient and it should correspond to the type of epilepsy.

For optimal treatment with phenytoin, the serum concentrations of the patient should be monitored at a specific time. In the case of adults, a concentration of 300 mg/day has the potential to produce either a too high or a too low concentration. It is recommended to monitor the phenytoin serum concentration two weeks after the onset of treatment.

During examination, it was established that, at the beginning, hyperplasia affected the interdental papillae, the free gingival margin and the attached gum. The lesions became generalized, predominantly in the frontal area, the arcade and the vestibular side of the dental crown, covering the entire clinical crown in 2 cases (18.20%).

In one case, the hyperplasic gum was pink, with an orange peel appearance, firm fibrous consistency and, due to satisfactory oral hygiene, small deposits of bacterial plaque.

In 2 cases (18.20%) the gum had an intense red color, a glossy smooth violet surface, edematous appearance and soft depressible consistency. It was detachable from the crown and there were large deposits of bacterial plaque, due to unsatisfactory oral hygiene. There were also deposits of supragingival tartar and local irritation factors.

The radiological examination of retro-dento-alveolar incidence (2 cases - 18.20%) indicates lack of bone lysis. In the case of parodontopathy with gingival hyperplasia (1 case - 9.10%), it was possible to observe the mixed lysis of the alveolar wall and the bone resorption degree.

From the histopathological point of view, several types of fibroblasts (passive and active) were determined due to the combined action of phenytoin and inflammation.

From the point of view of hyperplasic lesions, young patients predominantly present fibrosis with moderate inflammation; while in the case of elderly patients, inflammation prevails, achieving aspects of advanced periodontal injury.

In the case of *Ciclosporin A*-induced gingival hyperplasia (1 case - 9.10%), the histopathological aspects are similar to those induced by phenytoin, i.e., an epitheliomatous hyperplasia with deep intra-conjunctive crests.

In the corion, there is an abundant infiltration similar to the inflammatory one, predominantly plasmocites, together with an important increase in vasculature and increased collagen density. The inflammatory reaction is much more pronounced.

Cyclosporin A stimulates fibroblasts overcrowding and collagen accumulation due to the imbalance between synthesis and degradation activity.

In the case of *Nifedipine*-induced gingival hyperplasia, it has been localized at the teeth of the upper and lower left hemi-arcade teeth for about a year. The lesions started at the level of the interdental papillae and the marginal gum and extended later to the attached gum.

The histological examination of the biopsy harvested from Nifedipine-induced gingival hyperplasia shows: hyperkeratosis and parakeratosis; acanthosis in the spinous layer; epithelial dystrophic phenomena; elongation of the epithelial digitations inside the chorion.

All these epithelial changes are observed in the 7 cases (63.63%) that were studied, at the level of the papillary gum, free margins, sulcular gingival epithelium and the junctional epithelium.

At the level of the underlying lamineum, a dense, polymorphic, nonspecific inflammatory infiltrate was

observed, with predominance of lymphocytes and plasmocites.

One important thing for the etiological diagnosis of drug-induced gingival hyperplasia is that the lesions are reversible, sometimes almost completely, if a rigorous oral hygiene is applied shortly after discontinuation of the causal drug.

Differential diagnosis is made with other forms of gingival hyperplasia caused by local irritants or systemic disorders. The evolution of phenytoin-induce hyperplasia, especially in young patients, is less influenced by the presence of bacterial plaque and tartar, while Ciclosporin A and Nifedipine-induced gingival hyperplasia is aggravated by unsatisfactory oral hygiene, the inflammatory component of gingival hyperplasia is more important, the gum is swollen, deeply congested and sensitive to touch and it bleeds spontaneously.

Gingival hyperplasia lesions can be over-infected and present gum ulcerations covered by whitish deposits, purulent secretion in the periodontal pocket, accentuated swelling, congestion, bleeding and halitosis. The gum is very painful to the smallest touch, making it impossible to ensure proper hygiene. There is an increased accumulation of bacterial plaque, which maintains the inflammation.

Another aggravating evolution factor is oral breathing as a vicious habits that causes dry mouth and decreased salivary flow in Nifedipine-treated patients. That diminishes the possibility of self-cleansing, allows the accumulation of bacterial plaque and soft deposits and increases the incidence of caries, parodontopathy and Candida Albicans.

Therapeutic conduct : We insisted on prophylactic treatment. If the lesions had already appeared, we attempted a conservative treatment, in order to reverse the lesions or stop their progress, and if the lesions were spread and did not react to medical treatment, we proceeded to the radical surgical removal of the hyperplasic tissue.

Out of the 3 cases (27,27%) of *phenytoin* -induced gingival hyperplasia, where a prophylactic treatment consisting in the elimination of bacterial plaque and tartar was applied in order to reduce gingival inflammation, in 1 case (9.09%) the occurrence of gingival hyperplasia lesions could not be prevented in spite of good oral hygiene.

In 2 cases (18.20%) the surgical intervention consisted in gingivectomy by the classic technique of hyperplasic tissue removal and modeling of the gingival contour, by combined methods. Surgery was followed by rigorous oral hygiene.

Treatment of Ciclosporin A-induced gingival hyperplasia: In our case of gingival hyperplasia with severe gingival inflammation, we recommended antibiotic treatment (Azithromycin for 5 days and Metronidazole for 7 days) and chlorhexidine irrigations 0.12% in the periodontal pockets, which led to an improvement of the lesions.

Discontinuation of treatment leads to the reversibility of gingival hyperplasia, and just by reducing the dose of Ciclosporin A, it is possible to prevent the recurrence of gingival hyperplasia, even when the control of the bacterial plaque would leave much to be desired.

Treatment of gingival hyperplasia induced by calcium channel blockers- As far as drug treatment is concerned, the suppression of nifedipine seems to be the most effective method leading to a rapid regression of gingival hyperplasia.

In order to control bulky and generalized gingival hyperplasia, which persists even under rigorous control of the bacterial plaque, gingivectomy was indicated, followed by a good oral hygiene (5 cases - 45.45%).

Gingivectomy consisted in the excision of the gingival walls of the periodontal pockets, by removing the pathological elements from the pockets, the bone and the dental roots, in order to obtain a physiological gingival structure. It has the advantage of direct approach and visibility of the tartar and dental plaque, as well as of other elements of the periodontal pouch, allowing for their complete excision.

After gingivectomy, the wound is mandatorily protected with iodoformate meshes, which must be replaced after 4 hours. Healing is complete after 30-40 days. During that period, a new gingival ditch and a new epithelial junction are formed.

It is preferable to develop preventive and conservative measures.

Of the 11 studied cases, 3 cases (27.27%) wer subject to prophylactic treatment; 1 case (0.09%) drug treatment, and 7 cases (63.63%) surgical gingivectomy.

Conclusions

The diagnosis was based on the anamnesis, the clinical aspect of the lesions and the histopathological examination. After the surgical excision of the hyperplasia affected area, recurrence was prevented by dispensarizing the patients and controlling the bacterial plaque through rigorous oral hygiene

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