CYTOLOGY AND MOLECULAR MECHANISMS OF DRUG-INDUCED GINGIVAL HYPERTROPHY: A REWIEW

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SUMMARY
Introduction. Gingival hypertrophy is a frequent condition associated to the increased number of patients taking some categories of drugs. The goal of this work is to emphasize the importance of diagnosis to set a proper therapy.
Material and methods. The plaque accumulation in patients having a poor oral hygiene damages the periodontium and requires the application of strict professional and home hygiene protocols.
Results and conclusion. The drug-induced gingival proliferation knowledge is essential in order to succeed in working with the internist and in planning a precise therapy, without interfering with the metabolism of drugs, often necessary and irreplaceable for patients' health.

Key words: gingival hypertrophy, antiepileptics, CA-antagonists, cyclosporine, fibroblasts.

Introduction

The Periodontal Disease is a chronic degenerative inflammatory process of the periodontal tissue, whose pathological results are the loss of the connective attachment, the apical movement of the epithelium, the formation of periodontal pockets and the bone resorption of the alveolar process (1) (Figure 1).
Periodontology aims to study all congenital and acquired diseases, endogenous and exogenous, which involve the periodontium 4 components: gingiva, periodontal ligament, root cementum and alveolar bone proper.
The periodontium is not an organ but a complex bio-functional system which surrounds and composes the attachment and supporting tissue of teeth. Histologically, gingiva is composed by a keratinized, stratified squamous epithelium, with a connective tissue below, rich in fibroblasts able to product collagen (2). These cellular elements, together with dicationic ions, play a fundamental role in the cytological and molecular genesis of the oral mucosa hyper proliferative lesions.
The topic we are discussing will focus on the cytological and molecular mechanisms of the pathological increase of the gingival volume caused by drug therapy side effects. Our scientific contribute wants to underline the importance of anamnestic and clinical analysis of every data in order to establish the right operative protocol, specific for every patient, spotting the signs and symptoms, not only specific of the dental diseases but also of the related systemic diseases.
The mouth often represents the first alarm bell for general pathologies (Figure 2 a, b, c) even the more serious ones (4). The role of the dentist is to interpret those signs, collaborating actively with

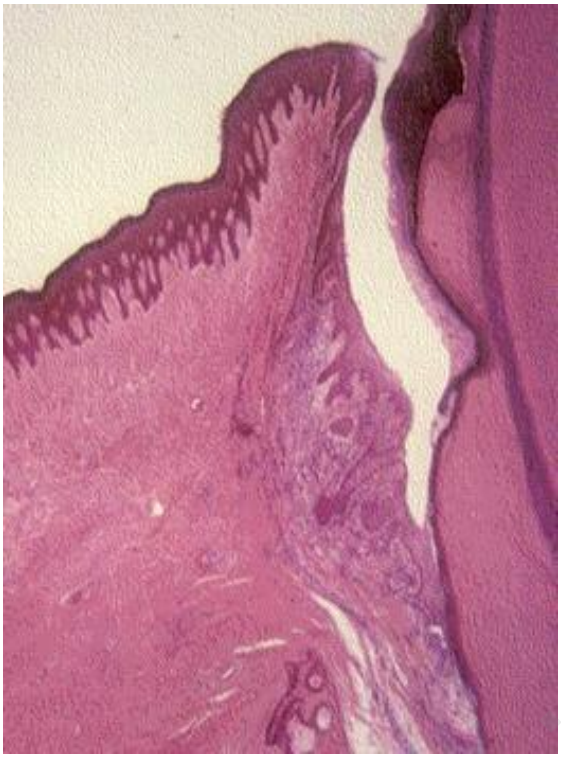

Figure 1
Histology of the periodontal socket.

fits. The epileptic fit is a sudden, excessive and rapid discharge of an electrical impulse of a certain population of neurons in the brain's grey matter (5). Those neurons involved in the electrical discharge form the epileptogenic focus. The antiepileptics are drugs that stabilize the electrical activity of the epileptogenic focus neuron cellular membranes, modulating the potential difference induced by the excitatory neurotransmitters (glutamate and aspartate) through Na+ channel blocking.

According to their action mechanisms, antiepileptics are divided in 4 categories:

- drugs that mostly inhibit the release of excitatory neurotransmitters (Phenytoin, Carbamazepine and Lamotrigine);
- drugs that increase the GABAergic transmission (Phenobarbital, Vigabatrin);
- drugs that stabilize the thalamic neurons (Ethosuximide);
- drugs that possess a combination of previous mechanisms (Valproic Acid).

The international literature shows a lot of confusion about this topic; no researcher in dentistry

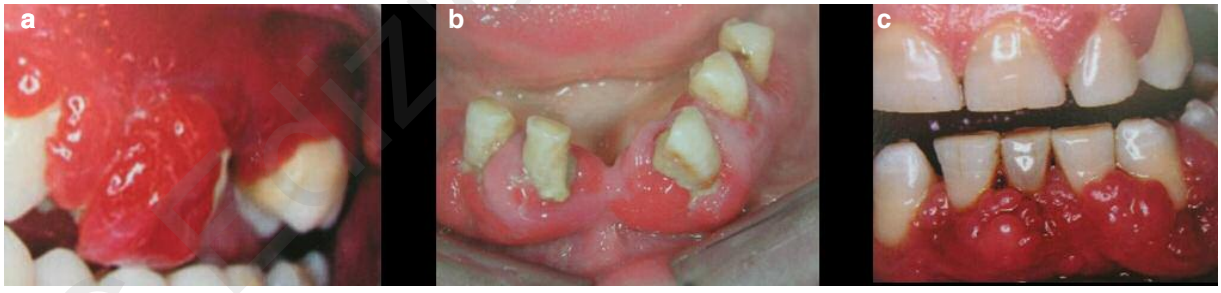

Figure 2
Sturg-Weber Syndrome (a), Diabetes mellitus type 2 (b), Leukemia (c).

the general doctors for the total health of the patient.

Discussion

Epilepsy is a neurological chronic condition characterized by recurring and sudden epileptic

has in fact explained the molecular mechanism by means of which this neurologically active metabolite can cause an increase of the gingival volume, maybe because among all the hyper proliferative drugs, it represents the one with the lowest rate of injuries incidence (5, 6). Therefore we have to consider the most accredited hypothesis made by molecular pharmacology: the above-named metabolite of the increased gingi-

val volume pathogenesis is 5,5-diphenil-dantoina.
This molecule, apart from its use in neurology, is also employed in the supraventricular arrhythmias induced by digitalis.
The blocking of sodium and chlorine channels, through the inhibition of excitatory neurotransmitters release, by means of the modulation of the glycine recognition site of N-methyl-D-aspartate receptor, puts into effect a series of ionotropic reactions, which, as a final result, would lead to a stimulation of gingival tissue fibroblasts that intensively synthesize collagen (much more type 3 instead of type 1), inhibiting the turn-over induced by the collagenases (5).
The block of sodium and chlorine electrolytic channels would lead to extra-cytoplasmic calcium releasing. Calcium, through c-AMP activation, causes the hyperexpression of Connective Tissue Growth Factor, which, by means of its action on fibroblasts, leads to the synthesis of substances such as integrin β-1 and β-6 that seem responsible of the hyper proliferative lesions of the oral mucosa in patients under chronic treatment with phenyl-dantoinic derivate (3, 4).
These lesions appear clinically peculiar (Figure 3): deep and pale red color, tough-elastic consistency, shiny, starting from the papillae, often covering ¾ of the entire masticatory surface (7).
The entity of the lesions is drug-dependent: after ceasing the molecule, they usually goes back to normal spontaneously even though very slowly; a certain help can be obtained by limiting at most the inflammatory action of local irritating factors (5).

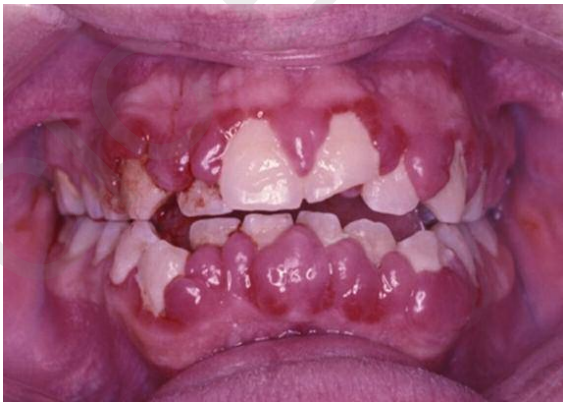

Figure 3
Gingival hyper proliferation caused by 5,5-diphenil-dantoina.

Calcium antagonists are pharmacological substances commonly employed in treating arterial hypertension and angina pectoris (Figure 5).
In recent years, the employment of Phenyl-Alkyl-Amine class (kind of calcium antagonist led by Verapamil), has shown beneficial effects on supraventricular arrhythmia, as an alternative molecule to β-blockers. According to their chemical nature, they are further subdivided in 3 groups:

1. Dihydropyridine: nifedipine, nitrendipine, etc…
2. Benzotiazepine: diltiazem etc...
3. Phenyl-Alkyl-Amine: verapamil, gallopamil, etc…

Recently, a second generation of dihydropyridine has been introduced in clinical cardiology: these drugs combine a major effectiveness with a minor incidence of side effects; in this category are part amlodipine, nicardipine and felodipine. These drugs inhibit the intracellular flow of Ca++, blocking the slow-gating channels, especially in the cardiac muscular tissue (Figure 4).
The lacking attachment of this ion inside of the sarcoplasmic reticulum inhibits the rapid depolarization of membrane potentials, working as a potential variation stabilizer (6). These molecules are absorbed by the duodenal mucosa (OS), then they get into the superior mesenteric artery and, through the portal vein, reach the liver, which, by means of the process of carboxyle groups methylation, activates the metabolites that are affected by the first step. Then they get in the blood stream with a bioavailability of the plasmatic proteins that varies from 70 to 95%, with T1/2=1,3/64 h. They are excreted by the kidneys through mechanisms of glomerular filtration (7). Their most frequent side effects are due to an excessive vasodilatation accompanied by vertigo, nausea, cardiovascular collapse and syncope.

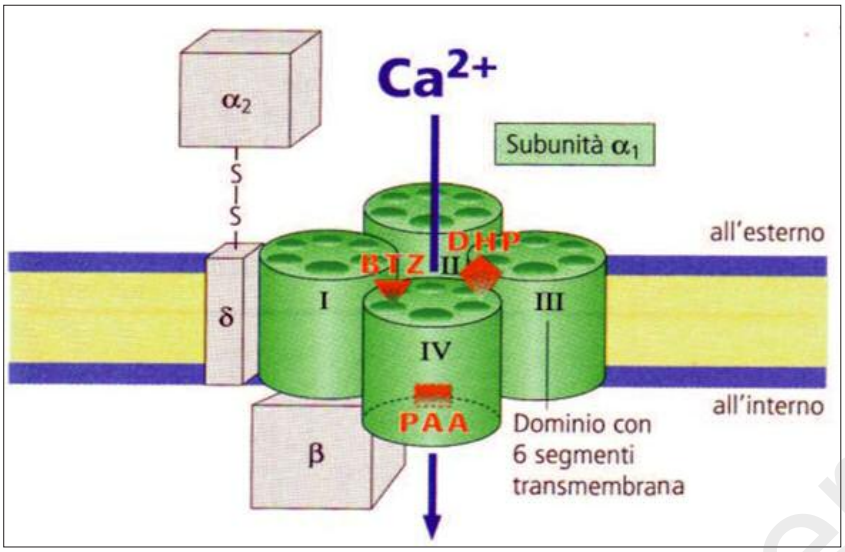

Figure 4
Calcium channel schematics that allows intracellular flow.

The dihydropyridine represented, until few years ago, the elective therapy for blood pressure swings; in the USA, 5 cases of stroke and 3 cases of IMA in the last 2 years were described, caused by excessive vasodilatation and uncontrolled increase of the afterload of the microcirculation associated with generalized hypoxia; the ADA current directions suggest the administration of furosemide sulfate 25 mg x Os until the hypertensive crisis is resolved. The active role of these molecules in the pathogenesis of gingival hyper proliferation induced by drugs, is likely to be carried out through their capability to increase the concentration of Ca^{++} ions inside fibroblasts (7, 8).
Some Authors suggested that these molecules are able to modulate the synthesis of cytokine such as IL-2, TGF-α and certain hormones such as testosterone, able to regulate collagen synthesis. Obviously, the diseases in need of these drugs make these hypertrophies mostly noticeable in elderly people (Figure 5).
The affected areas are the frontal element papilla. Hypertrophies rarely extend to cover the crown and often are very modest, very fibrous; sometimes they simulate the epulis formation, but they usually are formed by a collection of small nodules, giving the gum a papillary appearance. The multifocality of these injuries poses an explicit differential diagnosis with true periodontal neoformations (8).
Surgical techniques used to perform organ transplants have developed into a large scale since the 1900s and in the last few years have undergone continuous improvements to make such techniques extremely predictable.

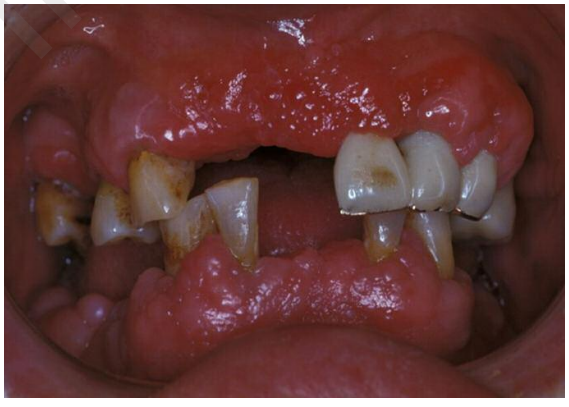

Figure 5
An elderly patient affected by gingival hyper proliferation induced by CA-antagonists. Notice the papilla aspect of the gingiva with multifocal lesions, which rarely cover the clinical crown.

During the post-operative period is necessary to give the patient a targeted drug therapy in order to suppress the immune response of the receiving body to any donor protein component, recognized as not-self. Among drugs that pharmacology has provided surgeons, there are some which have the side effect of inducing, in a certain percentage of cases, hyper proliferation of the gingival tissue (9).

In this category we find one of the drugs most commonly used in drug therapy anti-rejection: cyclosporine, a drug capable of inducing in the subject an immunosuppressive reaction. This molecule is a natural metabolic product of some funguses; it is the main therapeutic agent used to block rejection of any allogeneic transplant; it essentially works by blocking the transcription of cytokines in lymphocytes T. It was isolated for the first time in the Swiss laboratories of "Sandoz", obtained through the fermentation of the Agar broth of two funguses; Cilindrocarpon Lucidum and Trichoderma Polysporum.

Initially it was used as an anti-infective agent, then immediately emerged its immunosuppressive qualities (9, 10).

Cyclosporine is able to suppress the production of interferon and IL-2 by alternating the line of cell mediated support by lymphocytes T. This drug is unwieldy and its therapeutic window is very small, it's metabolized by the microsomal hepatic system, specifically by CYP-450, and then is excreted in the bile (10).

Its adverse effects are manifold, including renal hepatic toxicity, neurotoxicity, hypertrichosis and hyper proliferation of the gums. The gingival hypertrophy pathogenic mechanism seems to be answered in the ability of cyclosporine to modulate the expression of the receptors for the E.G.F at the level of the keratinocytes of the hypertrophic gingival tissue (4). This substance is able to work as a membrane stabilizer, increasing the concentration of Ca^{++} in the cytosol of fibroblasts. The molecular mechanism is rather complex: cyclosporine penetrates the plasma membrane, binds to a cytoskeleton contractile protein: the calmodulin physiologically binds Ca^{++}. In this way is inhibited the binding of calmodulin with calcineurina which modulates the reaction of cellular apoptosis (10, 11). Resulting in an inhibition of apoptosis with increased number of fibroblasts which, because of intracellular Ca^{++} increase, will be stimulated to the production of collagen; clinically this is translated as hyper proliferation of the gums (11). The lesions characteristically are bright red, glossy and crumbly texture, more present in the anterior sectors (Figure 6).

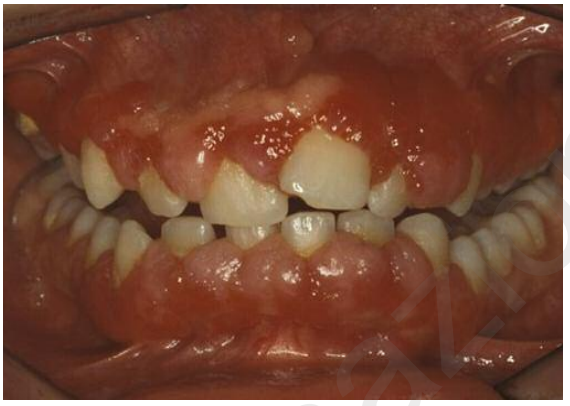

Figure 6
Patient subject to kidney transplant, under cyclosporine therapy.

It must however be recalled that cyclosporine is the drug of choice in kidney transplants, but causes, at the Loop of Henle, the release of high concentrations of Thromboxane - A2 with massive arteriolar constriction of the renal Rete mirabile.

This effect causes an increase in pressure, which is undesirable in patients with renal transplantation (12). To counter this negative effect the first choice drugs are CA-antagonists, which are excellent in reducing renal vasoconstriction, but combined induce significant gingival hyper proliferation, frequent and recurrent with summative and synergistic effect (4, 6, 9).

Conclusions

Because of its physiological and structural peculiarities, the oral mucosa, and in particular the marginal gingiva, constitutes an important and reliable indicator of generalized disorders of the organism, by the oral manifestations of particular systemic diseases, until the evolution of side effects related to the assumption of particular drugs (1). Although a molecule is administered correctly, each drug therapy presents a certain percentage of risk for the appearance of adverse effects, resulting from the assumption of a particular medical substance both in topical and systemic administration. It is widely known in the literature that the same drugs, including antiepileptics, immunosuppressant and calcium-antagonists can cause side effects such as gingival epithelial proliferation. Since the first appearance of these adverse effects, the research was stimulated to point out the pathogenic mechanisms in question according to which three heterogeneous groups, by their chemical and biological properties, could give the same side effects. Carefully analyzing the three pharmacological groups in question, it is possible to identify some common properties, especially the impact these molecules exert on periodontal tissue and their property to play the role of stabilizing the membrane potential. Clinically all descriptions of drug induced gingival hypertrophies present similarities: firstly appear outlines of fibrous thickening of the papilla, which gradually extends to the marginal gingival and the attached gingival; the anterior sectors result affected, maxillary and jaw, and more rarely it affects the posterior sectors. These thickenings concern only the areas in presence of teeth and gums, not affecting the edentulous areas (2). The thickening of the gums changes the anatomy of the emergence profile, canceling the auto-cleaning mechanisms to this overlap inflammatory phenomenon caused by increased difficulty in oral hygiene at home. Statistically however, despite the constant presence of bacterial plaque, not every patient under drug therapy develops an increased gingival volume. Therefore it has been suggested the presence of a certain genetic predisposition and increased individual reactivity. The complexity of the clinical management of these drug molecules is not within the competence of the dentist who must always interact with the specialist, who will assess the possibility of making arrangements or a replacement of the active ingredients, if possible without endangering the health of the patient (6). Confusion is often created in the daily dentistry practice, because of the incorrect interpretation of the same definitions as a result of the knowledge of basic medicine (8). Histologically, the increase in volume of the gingival mucosa is not identifiable with the definition of "hyperplasia" as there is not an increase in the number of epithelial cells; very often it is not correct to call this morbid state of "hypertrophy" because the cloudy swelling of the epithelial cells caused by the accumulation of calcium in the plasma, it is not present in all of its clinical forms.

The frequency reported in the literature varies from 14.3% up to 83.4% and differs depending on the pharmacological class, increasing the incidence in 20-25-year-old males, with a ratio of about 3:1 compared to female patients.

Therefore a fair number of cases, variable between 17 and 86% do not fall within the period of hypertrophy but it can be classified from the viewpoint of an anatomical and pathological gingival hyper proliferation (7). Their incidence increases significally when administered combination therapies such as those in support of patients with kidney transplants, when the immunosuppressant is crucial to avoid immunological reactions for the rejection of the organ, is associated with the calcium-antagonists to avoid an arterial hypertension of renal etiology. We can conclude by pointing out that the study of the pharmacological kinetics and dynamics is essential for any sanitary operator who has the need to administer to their patient drugs. Many of these drugs are metabolized within the hepatic microsomal system (Figure 7).

Our objective, as sanitary operators, is to raise awareness and stimulate professional and careful

Figure 7
Hepatic microsomal system: the universe of cytochrome P-450 with its most know isoforms highlighting the most known and studied ligands by the molecular pharmacology.

evaluation in total of the patient, whether be it from the clinical or semiological aspect as well, applying all dictated norms to a correct clinical methodology, without forgetting a single fact, focusing on the organic pathology and not just on the symptoms, because those are just the tip of the iceberg that threaten the health of the patient.

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