Non-Plaque Induced Diffuse Gingival Overgrowth

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gingival enlargement drug-induced gingival overgrowth acromegaly

1. Introduction

Non-plaque-induced gingival overgrowth (NPIGO) is part of a heterogeneous class of rare gingival modifications, due to a wide range of systemic conditions [1][2].

NPIGO can be due to hereditary factors, appearing as isolated forms (hereditary gingival fibromatosis) or part of a syndromic pattern [1][2]. It can also occur as a side effect of specific drugs consumption (Drug influenced Gingival Overgrowth—DIGO), such as: immunosuppressants, antihypertensives, anticonvulsant drugs and oral contraceptives; or it can be caused by hormonal alterations as occurs in pubertal gingivitis, during pregnancy or secondary to acromegaly [1][2]. Sometimes malignancies such as lymphoma and leukemia may arise in the oral cavity appearing as gingival enlargement too. However, in many cases, the NPIGO's etiology remains unknown, determining an idiopathic fibrous hyperplasia (IGF) [1][2][3].

NPIGOs' incidence varies in the population depending on the trigger agent. Genetic forms, both isolated and linked to syndromes, are very rare, with a prevalence of one case per 750,000 people [2][4]. DIGOs, have a higher prevalence, even if variable depending on the drug, ranging from 4% to 70% among patients taking these medications [5]. The prevalence of acromegaly in the population is about 50–70 cases per 1,000,000 people, of which around 70% develop a diffuse gingival enlargement [6][7].

The incidence of gingival involvement in patients affected by lymphomas and leukemias varies both on the basis of the tumors themselves and on the cell subtypes [8][9].

NPIGO has multiple clinical appearances, it is characterized by an abnormal increase in the gingival tissues that, in some cases, completely covers the teeth surfaces and causes serious aesthetic and functional issues [1][2][5][10].

According to the literature, the biggest issue of NPIGO (particularly the genetically determined ones) is represented by the diagnosis.

In fact, the challenge of making a differential diagnosis among many rare syndromes, the unavailability of complete genetic-molecular panels, together with the need for a multidisciplinary approach, makes the diagnostic pathway extremely difficult [2][3][5].

2. Drug-Influenced Gingival Overgrowth (DIGO)

Excessive gingival growth can be induced by a number of frequently used drugs, including antiepileptics, immunosuppressants and calcium channel blockers [2][5][11].

Among the antiepileptics, phenytoin, valproic acid, phenobarbital and carbamazepine are the most frequently involved.

Immunosuppressants are reported to cause gingival enlargement too: both cyclosporine and tacrolimus are well documented as possible triggers [2][5].

Among the calcium antagonist drugs, in addition to nifedipine and diltiazem, amlodipine, felodipine and verapamil may induce gingival overgrowth [2][5].

As previously reported, the incidence of DIGO varies according to the drug analyzed, ranging from 4% for some antihypertensives to 70% for antiepileptics such as phenytoin [5][12]. In the United States of America, approximately 1,000,000 people suffer from DIGOs [12].

DIGOs usually manifest as a diffuse increase in gingival volume, visible from 1 to 3 months after the first drug consumption [2][5][11][13].

These clinical data differ from hereditary gingival fibromatosis, in which there is a slow and progressive growth of the gingival tissues [5].

The extent of gingival growth can be mild to severe forms, in relation to the amount of medications taken [2][5][11]. Furthermore, the combined use of these drugs often has a synergistic action in generating more severe forms of gingival overgrowth compared to those triggered by a single drug [2][5].

Clinically, the gingival tissues show a granular appearance or a “cobble stones” aspect. The enlarged gingival tissues often cover the teeth, hindering oral hygiene practices and causing the accumulation of plaque [2][14]. These patients often present with chewing difficulties and aesthetic problems [2]. Overgrown gingiva may present with normal or erythematous discoloration [5].

These lesions can be associated with periodontal disorders such as bleeding and bone loss [2]. These problems are due to excessive gingival tissue which causes the formation of pseudo pockets with plaque accumulation [2][5][11][15]. Difficulty in carrying out normal oral hygiene maneuvers increases this vicious circle [2][5]. In **Table 1**, the clinical features of all drug-induced gingival overgrowth are listed.

Table 1. Clinical characteristics of Drug Induced Gingival Overgrowth.

Involved Drug	Clinical Characteristics
Antiepileptics (sodium valproate, phenobarbital, vigabatrin, primidone, mephenytoin and ethosuximide)	- First sign of enlargement affects the interdental papilla. - Gingival lobulations extend labiolingually and coronally to cover the entire anatomic crowns. - Tissue is dense, resilient, and may be stippled. - Presence of secondary inflammation may occur. - Teeth may be displaced, whereas generally the edentulous areas remain uninvolved. - In patients treated with phenobarbital, the gingiva grows globally and uniformly without lobulation of the papillae, and gingival lesions may be more severe in the posterior areas than in the anterior areas [16].
Immunosuppressants (cyclosporine and tacrolimus)	- Gingiva is markedly more inflammatory and the gingival bleeding is profuse. - Hyperplasia appears to begin in the interdental papillae and, more commonly, on the labial surface of anterior regions. - Lesions are generally limited to the keratinized gingiva that appears firm, with focal lobulations, having a stippled and pink surface. - Risk of chronic mycosis is possible [16][17][18].
Calcium antagonist drugs (Nifedipine, diltiazem, amlodipine, felodipine and verapamil)	- Gingival enlargement may appear as a firm nodular enlargement of the interdental papillae. - Anterior teeth are more affected than the posterior ones. - More pronounced on the facial/buccal than the palatal/lingual surfaces. -

Involved Drug	Clinical Characteristics
	In severe cases the entire papillae and the surrounding tissues are enlarged, giving the gingival tissues a lobulated appearance. - The overgrown tissue creates pockets that harbor pathogenic bacteria that are beyond the reach of a toothbrush or dental floss. Can lead to an increased host susceptibility to oral infection, caries and periodontal disease [19][20][21][22].
Oral Contraceptives	- Hemorrhagic and hyperemic gums. - Localized or diffuse increased volume. - Loss of periodontal attachment, possibly tooth mobility [23][24].

[5][13]

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From histological and cytological analyses reported in literature, it emerges that the lesions induced by phenytoin are characterized by an important fibrotic tissue component. The lesions induced by cyclosporine, on the other hand, present tissues with a predominant inflammatory component and few fibrotic outcomes. The lesions caused by nifedipine histologically show both the above-mentioned features [12].

Furthermore, cyclosporine, acting on cyclophilin and IL-2, attenuates the adaptive immune response, breaking the balance between adaptive and innate immune responses, and causing their enhancement [12]. Another element that has been documented is the attenuation of the apoptotic mechanisms induced by inflammation in all drug-induced lesions [12].

All these studies emphasize the hyperplastic nature of DIGOs and suggest that the amounts of inflammatory cells in these tissues differ according to the drug used [12].

2.1. Anticonvulsants

These drugs are used for the treatment of epilepsy and among all, phenytoin is the drug that in more than 50% of the patients causes gingival overgrowth [2][11][25].

The most suggestive hypothesis is that genetically distinct populations of fibroblasts react to phenytoin, resulting in an accumulation of connective tissue in predisposed subjects [11].

There is also the possibility that there is a reduced catabolism of the collagen molecules within the gingival tissue. Phenytoin has now been largely superseded by the new oral anticonvulsant drugs and is no longer recommended as a first-line treatment for epilepsy [2][11]. DIGO has also rarely been documented with other anticonvulsant drugs such as valproic acid, phenobarbital, and carbamazepine, that cause milder gingival volume increases [11].

2.2. Calcium Antagonists

Calcium antagonist drugs are used as a treatment for hypertension. About 20% of patients taking nifedipine and diltiazem experienced gingival overgrowth [11][26]. Other hypertensive drugs such as amlodipine, felodipine and verapamil may also be involved [11]. Excessive gingival growth in these patients is considered due to stimulation of the gingival fibroblasts, producing an increase in the connective tissue matrix secretion. Furthermore, a lower production of matrix metallo-proteinase is reported resulting in a reduction in protein turnover [11][17].

2.3. Cyclosporine and Tacrolimus

These drugs are often prescribed to patients who underwent or are waiting for an organ transplant [11][16]. It is documented that 30% of the patients who took cyclosporine experienced gingival overgrowth [11]. It is considered that the main metabolite of cyclosporine, hydroxy cyclosporine, stimulates the proliferation of fibroblasts, that increase in number while simultaneously decreasing the degradation of the gingival connective tissue [11]. Tacrolimus represents an alternative to cyclosporine, but it can also cause gingival enlargement, though less frequently than cyclosporine [11].

2.4. Oral Contraceptives

Oral contraceptives are one of the most commonly prescribed drugs and can be used in single (progesterone only) or combined (estrogen and progesterone) form [11][27]. The number of women taking oral contraceptives has reached around 50,000,000 worldwide and as a result of such extensive use of these drugs, many systemic and oral side effects have been identified [23].

Due to the high levels of estrogen and progesterone, women taking oral contraceptives present conditions similar to pregnant women, simulating the clinical characteristics of periodontitis [28].

The gums of these patients appear hemorrhagic and hyperemic, with a localized or diffuse increased volume and, in many cases, loss of periodontal attachment is present, possibly leading to tooth mobility [18][20][29].

Long-term treatment with oral contraceptive drugs is needed to see this kind of side effect [20].

Today gynecologists tend to prescribe low dosages of these medications, in order to reduce side effects: a correlation between dosage and adverse effects arising has been observed throughout [18][20][24].

High levels of progesterone increase blood fluidity which in the gums leads to greater sensitivity and vulnerability to bleeding [20].

Furthermore, progesterone and estrogen induce vasodilation, with a consequent increase in capillary permeability and greater migration of fluids and white blood cells out of the blood vessels [19][20].

Finally, changes in progesterone and estrogen levels cause immune alterations, as well as an increase in the production of collagen in the gums [19][20].

These alterations cause a reduction in the reparative efficiency and maintenance of the physiological gingival balance [20].

In addition, according to some studies, women taking oral contraceptives have a higher prevalence of Streptococcus mutans in the oral cavity and consequently a higher incidence of caries [20].

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