

Non-Plaque Induced Diffuse Gingival Overgrowth: An Overview

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Abstract: Non-plaque induced diffuse gingival overgrowth represents a broad class of conditions caused by several etiological factors. The aim of this review is to highlight the most recent updates and classifications of all the existent gingival overgrowths. In addition, we highlighted the diagnostic pathway that should be employed in patients affected by gingival overgrowth. Gingival overgrowth can be related to syndromic diseases including a wide spectrum of genetic and chromosomal alterations. However, thanks to scientific sharing and the availability of genetic panels it is possible to obtain an accurate phenotypic identification of well-known syndromes and also to identify new ones. This narrative review shows that through rigid, strict diagnostic protocols, the work of the clinician is greatly facilitated, despite the wide variety of pathologies considered. In conclusion, the exchange of specialists' competencies and the multidisciplinary management of these patients, are crucial to reach diagnosis and the correct clinical-therapeutic management.

Keywords: gingival enlargement; drug-induced gingival overgrowth; acromegaly; hereditary gingival fibromatosis; pubertal gingivitis; gravidic gingivitis; leukemic gingival enlargement; extra-nodal lymphomas of gingiva; diagnostic pathway in gingival overgrowth



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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) [1–3].

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].

The aim of this study is to classify the different forms of NPIGO, focusing particularly on the widespread ones, and to provide a guide for diagnosis.

2. Materials and Methods

This narrative review was conducted by reviewing articles published from 1950 to 2021.

The articles were selected according to their relevance, scientific validity, and quality, and were searched for in PubMed, Medline and Google Scholar using the following search terms:

- Gingival Overgrowth
- Gingival Fibromatosis
- Gingival Enlargements
- Gingival Hyperplasia
- Hypertrophic gingiva
- Gingival Elephantiasis

Articles included about treated diffuse gingival overgrowth, were in English, while review or duplicated cases were excluded. Finally, only 92 articles were analyzed and discussed in this narrative review.

3. 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)	<ul style="list-style-type: none"> - 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)	<ul style="list-style-type: none"> - 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 [16–18].
Calcium antagonist drugs (Nifedipine, diltiazem, amlodipine, felodipine and verapamil)	<ul style="list-style-type: none"> - 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. - 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 [19–22].
Oral Contraceptives	<ul style="list-style-type: none"> - Hemorrhagic and hyperemic gums. - Localized or diffuse increased volume. - Loss of periodontal attachment, possibly tooth mobility [23,24].

Although the clinical manifestations of DIGOs seem similar, the cellular and tissue characteristics vary according to the type of drug involved [5,13].

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].

3.1. 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 anti-convulsant 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].

3.2. 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].

3.3. 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].

3.4. 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].

4. Gingival Enlargement Induced by Hormonal Changes

4.1. Pubertal and Gravidic Gingivitis

Pregnancy has far-reaching systemic effects that extend beyond the reproductive organs. These effects are the end results of complex hormonal, immunological, dietary and behavioral changes that can exacerbate in the oral cavity causing gingival enlargement [2,30].

Excess gingival growth during pregnancy is a fairly common condition that affects 30% to 75% of all pregnant women [23,31].

Gingival enlargement in pregnant patients can be present both in localized and diffuse form and is characterized by mild or intense symptoms [2,11,23,24]. In this condition gums appear erythematous, edematous and hyperplastic with hemorrhagic diathesis tendency, and with spontaneous bleeding at the slightest stress [23].

Scientific evidence shows how an increase in circulating progesterone and estrogen alters the composition of the sub-gingival microflora, favoring more aggressive and destructive species [24].

In addition, the immunological alterations occurring during pregnancy make women more susceptible to pathogens such as *P. gingivalis*, *P. intermedia*, *A. actinomycetemcomitans* that overcome the host's defenses and become locally invasive [11].

Sex hormones act on neutrophils, reducing the effectiveness of phagocytosis and bactericidal mechanisms [11]. They also stimulate pro-inflammatory mediators such as E2 prostaglandins and endotoxins [11]. Finally, they cause an increase in vascular permeability and a reduced keratinization of the gingiva, which becomes more susceptible to stimuli [11].

The hormonal changes that occur during puberty can cause gingival overgrowth too [11]. These hormonal fluctuations generally affect adolescents of 12–14 years old, usually causing more localized and mild gingival enlargement than in pregnancy [11,32].

The gums of these patients will appear hyperemic, hyperplastic and edematous, especially in correspondence to the papillae, prone to bleeding and at risk of bacterial infections [2,11,33].

The pathogenetic mechanisms of pubertal and pregnancy gingival overgrowth are very similar, in fact in both an altered level of sex hormones is associated with an increase in gingival inflammation, with alteration of the gingival microflora and an increase in serum antibodies [11].

4.2. Acromegaly

Acromegaly is a rare disease with slow but progressive development, due to an excess of the growth hormone (GH) caused in more than 95% of cases by a pituitary adenoma secreting the hormone [34]. Hypersecretion of GH leads to the overproduction of insulin-like growth factor (IGF1) which results in a multisystem disease characterized by somatic overgrowth, multiple comorbidities, physical abnormalities and increased mortality [6,7,27,35,36].

The estimated prevalence of acromegaly is 50–70 cases per 1,000,000 people [6,27]. This disease generally arises between the 3rd and 5th decade of life with equal involvement of men and women [6]. The incidence of gingival volume increase in these patients is around 70% [7].

Acromegaly clinically appears with an enlargement of the major organs and with other alterations that can affect the oral cavity, such as thickening of the lips, prognathism, diastemas and hypercementosis, macroglossia and periodontal disease, with tooth mobility and loss [6,7,27,29]. Diffuse gingival volume increases were described too.

Macroglossia is a classic clinical sign of acromegaly, with enlarged furrows and dental impressions on the lateral edges of the tongue. It can cause difficulties in speaking [7].

Another typical feature of these patients is the median maxillary and mandibular diastema and is a very suggestive element for the diagnosis [7]. Changes in the size of the jaws and macroglossia are responsible for the formation of spaces between the incisors of acromegalic patients [7].

The increase in the length of the jaw is one of the most frequent findings in these patients. It is the consequence of an enlargement of the condylar cartilage of the temporomandibular joints [7].

Gum lesions in these patients are slow-growing and asymptomatic, presenting with a hard consistency and a light pink color and with a fibrous collagen component [6,7].

These are non-reversible alterations even after the correction of excess growth hormone secretion [7].

In acromegaly, gingival overgrowth is caused by alterations that act on three different levels: the increase in connective and epithelial volume, the secondary advent of inflammatory complications and the thickening of the alveolar edges due to the excessive influence of growth hormone [6].

5. Genetically Determined Gingival Enlargement

Hereditary Gingival Fibromatosis (HGF)

Hereditary gingival fibromatosis (HGF), also known as “gingival elephantiasis”, hereditary gingival hyperplasia or gingival hypertrophy is a rare benign disease characterized by a progressive increase in gingival tissue [3,37,38]. The gingival enlargement is due to an increase in submucosal connective tissue and occurs in different forms and severities [3,30,39].

It rarely appears at birth, more often with the eruption of deciduous or permanent teeth, and then worsens during adolescence and into adulthood [2,30,40–42]. Men and women are equally affected with an incidence of one case in 175,000 people [2–4,31,32,34,35,43].

Clinically, the lesions occur with a slow but progressive gingival overgrowth that can be localized or diffuse, with a preference for the tuber area, and the vestibular area of the molars [2,3,11,32]. However, involvement of the anterior jaw has been reported too [3].

The lesions are particularly thick and fibrous, very hard in consistency and in some cases extended beyond the surface of the teeth [2,11,31,32,44]. The inflammatory alterations tend to be negligible except for localized gingivitis and secondary to the accumulation of plaque [30,31,37,45]. Therefore, most of the lesions are neither hemorrhagic nor erythematous [3,30,31,35,37,38]. Tissues are light pink and nodular in appearance, with some documented exceptions [3,30–32,35,37,38].

The gum's enlargement causes both aesthetic and functional problems [3,10,30,31,34,35,37]. The most common effects are diastema, malposition of the teeth, prolonged retention of teeth, delays in eruption, cross and open bite, prominent lips, and a tendency to keep the mouth open at rest [3,10,30,31,34,37].

Although HGF does not directly affect the alveolar bone, gingival growth can cause the formation and accumulation of plaque, leading to a greater risk of developing periodontal disease, bone resorption and halitosis [3,30,34,37,46].

Traumatic chewing injuries, due to the bulk of enlarged gingiva, are also frequent [11].

A mutation in the Son of Sevenless-1 (SOS-1) gene has been identified on chromosome two as an etiological agent [4,11,38,47,48]. A deletion mutation introduces a premature stop codon into the encoding of the SOS-1 sequence. This mutation creates a modified SOS-1 protein that is more active than wild type SOS-1. SOS-1 is functionally important in signal transduction, in the cellular growth, differentiation and division control [40]. SOS-1 is expressed by many cells in different tissues, but it is particularly highly expressed in gingival tissue [40].

Studies on the gums of individuals affected by HGF showed an increase in the amount of collagen, number of fibroblasts and tissue proliferation rates. They also showed that

there are modifications in the signal transduction of fibroblasts associated with the SOS-1 mutation in patients with HGF [40]. Mutated SOS-1 can move towards the plasma membrane without stimulation of the growth factor, leading to prolonged activation of RAS/MAPK signaling [40]. The consequent rise of the amplitude and duration of ERK signaling and the enhancement of phosphorylation of some proteins in the nucleus are associated with the upregulation of cell cycle regulators and the transcription factors that promote cell cycle progression from G to S phase [40].

However, several studies indicate genetic heterogeneity as the cause of HGF. In fact, while the SOS-1 gene mutation is etiological for some cases of gingival fibromatosis, other cases are caused by other types of genetic alterations such as chromosomal abnormalities [40].

HGF can be an isolated form or be part of a more complex multiorgan syndromic picture [2,3,41].

The syndromic traits accompanying HGF are usually autosomal recessive, while isolated HGF generally have autosomal dominant modes of inheritance [2,3,32,35].

The syndromic forms reported in the literature are listed in Table 2, together with the clinical description of the associated gingival overgrowth. Most of them have hereditary traits, with only the exception of the Sturge-Weber Syndrome, which is caused by a non-transmissible somatic mutation.

Table 2. Syndromes related to gingival overgrowth.

Syndrome	Clinical Manifestation of the Gingival Enlargement
Prune-Belly Syndrome	<ul style="list-style-type: none"> - Important increase in the volume of the adherent gingiva, of the maxillary tuberosities beyond the retromolar pad [42]. - Total over-encirclement of both upper and lower teeth by the gingiva, with the only exception of the central deciduous teeth [42]. - Hard consistency of hyperplastic gingival tissues [42]. - Light pink in color without evident areas of inflammation and which tend to white following acupressure [49].
Schinzel-Giedion Syndrome	<ul style="list-style-type: none"> - Massive gum growth compressing the tongue on the pharynx, surrounding completely the teeth and causing the patient difficulty in swallowing and breathing [50].
Hurler Syndrome (Mucopolysaccharidosis type I)	<ul style="list-style-type: none"> - Gingival overgrowth is a constant feature [44]. - Gingiva shows a nodular appearance and a more intense color than the normal gingiva, in some cases with hemorrhagic tracts [51]. - Tends to cover all the dental elements except for the anterior centrals [44].
Maroteaux-Lamy Syndrome (Mucopolysaccharidosis type VI)	<ul style="list-style-type: none"> - Gingival hyperplasia and hypertrophy of the maxillary alveolar ridge are considered one of the main oral manifestations of this syndrome [52].
Schie and Hurler/Sheie Syndrome	<ul style="list-style-type: none"> - Represents a milder form of type I mucopolysaccharidosis [44].
Hunter Syndrome (Mucopolysaccharidosis type II)	<ul style="list-style-type: none"> - Clinical features similar to Hurler's Syndrome, but milder [44].
Ehlers-Danlos Syndrome	<ul style="list-style-type: none"> - Particularly in EDS subtype VII [32,53]. - Gingival overgrowth arises in the first months of life [32,46]. - The gums appear fragile, highly inflamed, and hemorrhagic, with very aggressive forms of periodontal diseases leading to bone resorption and the loss of dental elements [32,46].

Table 2. Cont.

Syndrome	Clinical Manifestation of the Gingival Enlargement
Costello Syndrome	<ul style="list-style-type: none"> - Patients frequently present thickening of the posterior maxillary alveolar ridge, and cases involving the anterior mandibular alveolar ridge are also documented [54,55]. - 64% of these patients have gingival hyperplasia [47]. - Gums have a pink color and a hard texture [48]. - Possible partial or total coverage of the dental elements (especially posterior) by the gingiva [47,48].
Mucopolipidosis II (I-cell disease)	<ul style="list-style-type: none"> - Marked enlargement of the gums and alveolar processes, making the lower part of the face profile appear in the shape of a “fish” [56,57]. - Gingival overgrowth is progressive starting from 4 months of age [49,50]. - Open bite caused, when the patient tries to close the mouth and contact occurs only in the back of it [49,50]. - X-ray examination of the jaws shows that the dental elements are completely buried inside the gums and commonly do not erupt [49,50]. - Gingival tissues are soft and slightly elastic with a vertical growth direction [49,50].
Aspartylglucosaminuria	<ul style="list-style-type: none"> - Less extensive than other gingival enlargements [58,59]. - High incidence of gingival overgrowth, although not a direct cause of lysosomal accumulation due to aspartylglucosaminuria, could be due to an important inflammatory response triggered by abnormal tissue metabolism. For this reason, the gingival tissues of these patients are clinically compatible with gingivitis [51,52].
Alpha-mannosidosis	<ul style="list-style-type: none"> - Few documented cases in literature [53]. - Nodular hyperplastic lesions of hard consistency, slightly erythematous of different sizes, caused by the infiltration of histiocytes into the gingival level are described [60].
Menkes Kinky Disease	<ul style="list-style-type: none"> - Upper and lower bilateral gingival overgrowth with delay in the eruption of dental elements related to important gingival development [45,46]. - Marked inflammatory component is not described [45,46]. - Gingival color and consistency appear to be normal [61,62].
Ligneous periodontitis	<ul style="list-style-type: none"> - Gum lesions of this pathology are a direct consequence of the plasminogen deficiency which reduces the natural fibrinolysis causing fibrin deposits. These alterations lead to the formation of mucous pseudo membranes which alter the gingival tissue, and which tend not to heal becoming subject to bacterial superinfections [63,64]. - Gums have a nodular appearance with numerous ulcers and periodontal lesions that over time lead to mobility and subsequent loss of dental elements [56,57].
Cowden Syndrome	<ul style="list-style-type: none"> - Oral lesions are present in 80% of patients and are considered as a major diagnostic criterion, especially for early identification of the disease [32]. - Gum lesions consist of small and multiple pink or whitish papules or nodules of approximately 1 to 3 mm [32]. - Lesions can be isolated or merged, giving a characteristic cobbled appearance [32].
Zimmermann-Laband Syndrome	<ul style="list-style-type: none"> - Gingival hypertrophy is the most explicit clinical aspect of this syndrome, leading to chewing, aesthetic, and functional difficulties [58]. - Usually occurs at birth or after a few months [58]. - Slow and progressive development of the maxillary and mandibular gingiva [65].

Table 2. Cont.

Syndrome	Clinical Manifestation of the Gingival Enlargement
Juvenile systemic hyalinosis	<ul style="list-style-type: none"> - Gingival tissues can completely cover the deciduous teeth [66,67]. - Gums have a soft and inflamed texture [59,60]. - Difficulty in maintaining adequate oral hygiene leads to a high incidence of carious lesions, with patients having difficulty in feeding precisely because of odontogenic pain [59,60].
Cantú Syndrome	<ul style="list-style-type: none"> - Gingival hypertrophy inducing an open bite in the affected patients for the pre-contact of the posterior gingival tissues [68–70].
Jones Syndrome	<ul style="list-style-type: none"> - Gums have a hard, fibrous consistency, with a color ranging from pink to red, secondary to the presence of inflammation [71,72]. - Gingival overgrowth is widespread and affects both the posterior and anterior sector [64,65]. - Gums tend to cover the dental elements causing problems of an aesthetic but also functional type [64,65].
Hypertrichosis Gingival Fibromatosis Syndrome	<ul style="list-style-type: none"> - Gingival fibromatosis is a major component [66]. - Increase in gingival volume leads to chewing difficulties [66]. - Gum is pale pink in color and fibrous in consistency and can be extended to all surfaces of the teeth [73].
Ramon Syndrome	<ul style="list-style-type: none"> - Gingival fibromatosis is a constant feature [74,75]. - Gingival enlargement is painless, spreads over both arches and the dental elements appear totally or partially covered by the gum [67,68]. - Gum shows a normal color and a hard consistency [67,68].
Juvenile hyaline fibromatosis	<ul style="list-style-type: none"> - Same clinical characteristics as that found in the juvenile systemic hyalinosis [59].
Oculo-dental type Rutherford Syndrome	<ul style="list-style-type: none"> - Gingival hyperplasia is one of the three most evident manifestations [69]. - Gums have a normal color and hard consistency [69]. - Dental elements are totally covered by the gingival tissues [76].
Nephrocalcinosis Amelogenesis Imperfecta (Enamel-Renal Syndrome)	<ul style="list-style-type: none"> - Gingival hyperplasia is one of the major clinical findings [70]. - Gums are normal in color and hard in texture [70]. - Dental elements are often not clinically visible [77].
Syndrome Amelogenesis imperfecta-gingival fibromatosis	<ul style="list-style-type: none"> - Important inflammatory component and partial or total coverage of the dental elements by the gingiva [78]. - Difficult to carry out hygiene maneuvers with consequent accumulation of plaque and an increase in the inflammatory component [71].
Sturge Weber Syndrome	<ul style="list-style-type: none"> - Hemangiomas are typical signs [32]. - Hemangiomas appear bright red or purple in color and are placed unilaterally and rarely cross the midline [32]. - Lesions present with gingival hyperplasia secondary to an increase in the vascular component [32,40].

Table 2. Cont.

Syndrome	Clinical Manifestation of the Gingival Enlargement
Neurofibromatosis	<ul style="list-style-type: none"> - Gingival enlargement is a common manifestation in patients with type 1 neurofibromatosis [11]. - Gingival overgrowth affects both children and adults [11]. - Lesions are one-sided and generally painless [11]. - Signs of inflammation are almost absent [11]. - Gingival tissue tends to be hard, but cases with soft gum lesions are also documented in the literature [11,32,79,80]. - Patients may present impacted or misplaced teeth and with agenesis [11,72,73].
Facial dysmorphism, hypertrichosis, epilepsy, intellectual/developmental delay, and gingival overgrowth syndrome (FHEIG)	<ul style="list-style-type: none"> - Mutation of the KCNK4 gene has recently been identified, leading researchers to describe this new syndrome [62,74]. - HGF is always among the main clinical manifestations varying according to the severity of the disease [62,81]. - Gingival tissues are significantly enlarged with a nodular appearance and a pinkish color [62]. - Dental elements are totally enveloped by the gingival excess [62,74].
Acromegaly facies hypertrichosis syndrome (HAFF) And Acromegaly facies syndrome (AFA)	<ul style="list-style-type: none"> - Gingival hyperplasia is documented among the various clinical manifestations [75]. - Clinical features vary according to the severity of the disease but are similar to other non-inflammatory syndromic forms with normal color of the gums which, however, appear to have increased volume [82].

Drawing a common line of the anomalies manifested by these patients would be very difficult due to the heterogeneity of the clinical features [34].

However, some traits such as mental retardation, hypertrichosis, craniofacial and skeletal anomalies appear to be recurrent in the different syndromes [35,36,38,39].

6. Idiopathic Gingival Fibromatosis

Idiopathic fibrous hyperplasia or idiopathic gingival fibromatosis is characterized by a slow but progressive benign gingival overdevelopment affecting the marginal gingiva, the adherent gingiva, and the interdental papilla. This condition affects one in 750,000 people and targets both sexes equally [5]. Clinically it is indistinguishable from HGF and other widespread forms of gingival overgrowth, but it is neither comparable nor attributable to any of the previously listed syndromes, nor to isolated HGF, nor to other forms of gingival enlargement [2]. However, there are documented cases in the literature, with the diagnosis of idiopathic fibrous hyperplasia and clinical histories, that also present traits similar to multi-organ syndromic alterations previously mentioned. Not meeting all the diagnostic criteria necessary to assimilate them to syndromic alterations, they are diagnosed as idiopathic gingival fibromatosis, therefore the diagnosis is made by exclusion [2]. Several authors hypothesized the existence of ex novo mutations in these patients therefore not phenotypically identifiable in the closest relatives and leading to the diagnosis of idiopathic gingival fibromatosis [2].

7. Leukemias and Lymphomas

Leukemias are a group of malignant hematopoietic disorders characterized by an abnormal proliferation and development of leukocytes and their precursors in the bone marrow [8,11]. This disease is classified into acute or chronic forms based on its clinical behavior, and into myeloid and lymphoid depending on the histo-genetic origin of cells [8].

Oral lesions from leukemia represent a very frequent complication, as they can be premature manifestations of the disease and therefore important for an early diagnosis [11,83].

The incidence of this neoplasm is very high, being considered the most common hematological white blood cells tumor, with an incidence of nine cases per 100,000 people. Moreover, leukemia accounts for 30% of malignancies diagnosed in children under the age of 15 [76].

The gums of these patients are enlarged, bleeding and pale in color; ulcerative lesions may also be present [15,32,35,49].

These oral manifestations may be the result of the infiltration of leukemic blasts into the gingival tissues or secondary to thrombocytopenia, neutropenia, or impaired granulocyte function [11,13,76].

Subtypes of leukemia are defined based on the cells of origin (myeloid or lymphoid) and the stage of differentiation [11,76].

7.1. Acute Myeloid Leukemia (AML)

Acute myeloid leukemia accounts for approximately 25% of all types of leukemia. Clinical manifestations are related to the complications of pancytopenia. The gums of these patients are pale due to anemia, with a bleeding and hyperplastic tendency due to the infiltration of leukemic blasts. Gingival manifestations can be an early sign of the disease. The extent of the gingival overgrowth may vary according to the stage of the disease, being able to cover the surfaces of the dental elements partially or completely and thus causing aesthetic and functional problems [76].

7.2. Chronic Myeloid Leukemia (CML)

Chronic myeloid leukemia is one of the most common myeloproliferative disorders in adults between 30 and 50 years old.

It accounts for 20% of all cases of leukemia, and it is characterized by the presence of many well-differentiated cells in the bone marrow, peripheral blood, and tissues with a prolonged clinical course.

The oral manifestation and specifically the gingival ones are rare; and widespread increases in gingival volume are documented in the few cases present in literature [76].

7.3. Acute Lymphoblastic Leukemia (ALL)

Acute lymphoblastic leukemia represents the most common malignant neoplasm in the pediatric age, but it can also affect adults. It is characterized by an uncontrolled proliferation of hematopoietic progenitor cells which leads to a high number of circulating blasts, replacement of the normal marrow by these cells and infiltration of the same in multiple organs.

Oral manifestations can be early and associated with pancytopenia and the infiltration of leukemic blasts into the tissues. The gums are directly affected and appear to be pale, bleeding and increased in volume. Some authors described the gingival overgrowth as the first manifestation of the ALL [76].

7.4. Chronic Lymphocytic Leukemia (CLL)

Chronic lymphocytic leukemia represents 25–30% of all types of leukemia, with an involvement of the oral cavity in 5% of cases. The subjects most affected by this disease are over 55 years of age.

Oral lesions usually appear at advanced stages of the disease; therefore, they do not represent an aid for an early diagnosis. Gingival enlargement, bleeding, pain, and ulceration are frequently described oral manifestations. [76].

7.5. Lymphomas

Lymphomas are tumors of the lymphoid system and represent the most frequent hematological malignancies [9]. They can originate from B or T lymphocytes and their lines of development. There are two types of Lymphomas: Hodgkin's Lymphomas and Non-Hodgkin's Lymphomas [41,84]. Lymphomas are the second most frequent malignant

neoplasms in the head and neck area and represent 3.5% of malignant neoplasms of the oral cavity [9]. According to various studies, the gum appears to be the most frequently affected site of the oral cavity, after Waldeyer’s ring [9,77]. The average age of the patients is over the seventh decade of life [9,77].

The subtype that most frequently affects the mouth is B-cell non-Hodgkin’s lymphoma followed by T-cell NHL [55,60,64]. Oral manifestations of Hodgkin’s lymphoma are very rare [2,41,85].

Other oral subtypes documented are Burkitt’s lymphoma, lymphoblastic lymphoma, extra nodal natural killer cell lymphoma, marginal zone B-cell lymphoma, mantle cell lymphoma, plasmablastic lymphoma, and lymphoblastic lymphoma [77].

The gums of these patients have an increased volume due to the infiltration of the monoclonal tumor components that occurs through the blood. They tend to be painless even though cases of patients with widespread pain were reported [9,77,86]. The lesions are described as basically non-bleeding, with exceptions probably related to thrombocytopenia of the advanced stages of the disease or due to chewing trauma due to gingival overgrowth [77]. According to the studies, most of the cases were diagnosed in stage I and II, making early diagnosis very important for the treatment of these conditions [9].

All the most salient clinical features of gingival lesions secondary to lymphomas and leukemias are shown in Table 3.

Table 3. Clinical characteristics of leukemias and lymphomas related gingival overgrowth.

Clinical Characteristics	
Acute Leukemia (acute myeloid leukemia, acute lymphoblastic leukemia)	<ul style="list-style-type: none"> - Gingival bleeding. - Gingival hyperplasia. - Ulcers and petechiae. - Mucosal pallor related to anemia [83,87,88].
Chronic Lymphocytic Leukemia	<ul style="list-style-type: none"> - Oral manifestations of CLL are related to an advanced stage of a diagnosed disease, so that they can not be employed to advantage for making an early diagnosis. - Local swelling, with or without ulceration and pain. - May also be associated with recurrent oral bleeding [83,88].
Lymphomas	<ul style="list-style-type: none"> - Non-bleeding lesions. - Gingival hyperplasia. - Increased tooth mobility. - Progress rapidly. - Oral manifestations may present as the first and only sign of disease. - Asymptomatic soft swelling [84,89,90]

8. Diagnostic Pathway in Gingival Overgrowth

The diagnostic pathway of patients with NPIGO can be complex. It is therefore important for the clinician to scrupulously investigate possible causes of gingival overgrowth, discarding through differential diagnosis all the pathologies previously mentioned, and if necessary, investigating the nature of the gingival enlargement with multidisciplinary management and specific exams [5].

8.1. Anamnesis

First, an accurate anamnesis is fundamental. Patients must be questioned about their family medical history with reference to surgeries and/or pathologies that have affected their close relatives, any gingival enlargement and/or manifestations linkable to one of the previously listed syndromes [11,31]. This is crucial when a syndromic or isolated HGF is suspected [5,11,31].

Secondly, it is important to proceed with the patient's physiological anamnesis, investigating somatic growth, his/her lifestyle habits, physiological functions, daily life environment from birth up to the present. This type of information on the patient's somatic growth allows evaluation of their birth conditions, breastfeeding, teething, deambulation, puberty, menstrual cycle [11].

The questions regarding daily environment must explore the patients working and school conditions, while questions on lifestyle give details whether the patient uses alcohol or smokes or takes drugs [11]. Information regarding patients' physiological functions give a picture of the types of diet, the sleep habits, the frequency of miction and the regularity of the bowel [11]. Equally important for the clinician is to be informed about the patient's medications, and the times of both intake and any possible suspension: in fact, it is DIGOs that appear after about 3 months of consumption [11].

No less important is the patient's remote pathological anamnesis, that describes both the general and dental clinical history, particularly regarding previous oral surgery and the onset of severe disease [11].

Finally, the close pathological anamnesis is carried out to obtain information regarding appearance, symptoms, and duration of the lesions [11]. This is another crucial element regarding the differential diagnosis between both drug induced forms, or hormonal, and neoplastic and genetic ones [11]. In particular, the genetic forms are already present at 3 years of age while the neoplastic ones (except for acute lymphoblastic leukemia) or the conditioned (depending on the etiological agent) tend to develop later in life. The rapid manifestation of gingival overgrowth, especially in older age, without apparent causes attributable to patients' habits, such as use of drugs, poor oral hygiene, or other causes, should alert the clinician to carry out more tests, as there will be a strong suspicion of an oral manifestation of a neoplastic pathology [11].

8.2. Clinical Examination

The clinical examination plays a fundamental role in the management of patients with diffuse gingival volume increase not induced by plaque. Together with the medical history and laboratory tests, it helps to assess whether the condition is hereditary or acquired and the presence of other diseases [34,38].

Extra-oral and intraoral clinical examination must be performed.

The extraoral clinical examination distinguishes and identifies syndromic HGFs. As described above, these syndromes present a series of common characteristics and other elements typical of each syndrome. Therefore, the clinician needs a complete and comprehensive overview of the patient, assessing not only what he sees in the oral cavity, but the patient as a whole. For this reason, the clinician should have competences of general medical practice that could address the patient through a multidisciplinary approach with the support of other professionals from different specialties interested in the syndromes treated [5,38].

The intraoral clinical examination assesses the extent of the gingival enlargement [38]. According to the classification made by Glickman et al., a gingival overgrowth is diffuse when it involves the gingival margin and the rest of the gingival mucosa up to the mucogingival fold and for a variable distance along the lingual/palatal surface [1].

NPIGOs all have very similar clinical aspects. Exceptions are some neoplastic forms showing gingival bleeding, erythema, and a bright red color of the gum (especially marginal). In other cases, the gingiva will have a pink aspect, hard consistency, with a non-hemorrhagic diathesis except for superinfections or overlapping gingivitis [9].

The clinical examination, together with family history and histological exams, is extremely important for the diagnosis of isolated HGF for which, according to various studies, there is no indication to carry out genetic tests to confirm the diagnosis [2,4,5,31,34,38].

For the intraoral clinical assessment of the size of the gingival enlargement two complementary indices can be used: the vertical index GOi and the horizontal index of Miranda and Brunet (MBi) [91].

The GOi measures the height of the gingival tissues in the apico-coronal direction from the CEJ to the free gingival margin [80]. This index allows evaluation, with the use of a periodontal probe, the height of the gum in the gingival overgrowth and the degree of partial or total coverage of a dental element using six criteria [80]:

- 0 mm = normal gingiva
- 1 mm = slight increase
- <2 mm = the gingiva covers the cervical third or less of the anatomical crown
- 2 mm = moderate increase of 2–4 mm with gingiva extended in the middle third of the clinical crown
- 3 mm = severe
- >4 mm = the gingiva covered more than 2/3 of the clinical crown

The MBi, also known as the nodularity-papilla index, measures the horizontal enlargement of the papilla from the tooth enamel surface or from the interdental point of contact of the teeth to the outermost portion of the papilla surface in the buccal direction [80]. Also, in this case, the periodontal probe is used for the measurements and two ratings are considered, one for the buccal papilla and one for the lingual-palatal papilla according to the following criteria [80]:

- 0 mm
- <1 mm
- 1 mm
- 1–2 mm
- 2 mm
- >2 mm

According to Beaumont et al. a simple grading system can be used to describe the extent of the gingival enlargements [11]:

- 0 = No sign of gingival enlargement
- 1 = gingival enlargement confined to the interdental papilla
- 2 = gingival enlargement involving the papilla and the marginal gingiva
- 3 = gingival enlargement surrounding $\frac{3}{4}$ or more of the crown of a tooth

Grading and the extent of inflammation can provide important data on etiology [11]. A hard, fibrous, pink, homogeneous consistency gingival overgrowth indicates no inflammation [11]. This, as previously mentioned, is more frequent in patients with HGF, or in DIGO patients, in cases secondary due to hormonal changes and in patients with excellent oral hygiene [11]. In cases where plaque-induced inflammation is present, the appearance of the gum is more likely to be smooth, shiny, and reddened [11].

8.3. Laboratory Tests

Laboratory tests are of fundamental importance for the clinical diagnosis of acromegaly and in case of clinical suspicion of lymphomas or leukemia [5].

In the specific case of acromegaly, the clinical diagnosis is confirmed by the rise of GH serum concentration and by the assessment of the increase in the levels of the insulin-like growth factor (IGF-I) [7]. The volume and extent of neoplasms are then assessed through instrumental tests such as magnetic resonance imaging [7].

Regarding the neoplasms that can occur with diffuse gingival overgrowth, laboratory tests are not useful for diagnostic purposes, but they can help the clinician in the differential diagnosis with the different forms of gingival enlargements [5]. Specifically, these cases will show altered values of red blood cells, white blood cells, platelets as well as alterations in the erythrocyte sedimentation rate (ESR) and increased levels of lactate dehydrogenase (LDH) [2].

8.4. Imaging

Instrumental examinations play an important role in the intraoral assessment of gingival enlargements.

Among the first level exams, above all orthopantomography x ray could be necessary for the evaluation of the presence or absence of dental and supernumerary elements [34].

It should be mentioned that many of the genetic diseases associated with gingival enlargement can also manifest in the oral cavity with agenesis or supernumerary teeth [34].

Second level examinations, such as MRI or CT, are mostly used for the detection of bone and soft tissue lesions, secondary to genetic multiorgan diseases, acromegaly, or malignant blood neoplasms [34].

8.5. Genetic Tests

If the medical history, clinical examination, and laboratory tests lead to suspicion of a genetic disease, the patient's closest relatives are directly evaluated both from an anamnestic and clinical point of view [5]. It is therefore also possible to draw up a genealogical chart to determine if the anomalies constitute an isolated entity or coexist with another disease or syndrome. At this point, the clinician must be supported by the geneticist for further clinical examinations and undertake genetic diagnostic tests [5]. These tests are essential to reach a diagnosis, for rare syndromic forms [5]. However, it must be said that not all syndromic HGFs are diagnosed through genetic tests. For many of these, certain clinical criteria are sufficient [31,34]. In any case, the goal of understanding the genetic basis of the disease is not only to facilitate the diagnosis but also to target the treatment to correct specific biological defects affecting each individual patient [40,92].

8.6. Histopathological Examination

The biopsy and the consequent histopathological examination are used to provide the clinician with useful elements for diagnostic purposes and therefore for a further understanding of the nature of the lesions. This examination is usually carried out after an initial management phase of these patients, especially if there is no type of improvement in the gingival enlargement [11].

In reference to a gingival lesion suspected to be secondary to a hematological malignancy, biopsy should be performed with caution or avoided, due to the risk of bleeding and infection secondary to pancytopenia. Several studies have shown that in some cases the use of cytological examination (FNAC) can be simpler and safer [5,13].

Concerning isolated HGFs associated with syndromes, the attention in reading the histological examination is mainly focused on connective tissue changes [3]. The tissues affected by HGF show an important increase in collagen fibers associated with some fibroblasts [3].

However, it should be considered that, as emerges from the literature, the histological aspects of HGF are non-specific and that the definitive diagnosis should be based on family history, clinical findings, and genetic investigations [3]. With reference to the histological examination, Table 4 lists the indications for performing a biopsy. In addition, a summary of the most important features of all the gingival overgrowth treated, is listed in the same table.

Table 4. Analogies and differences between different types of non-plaque induced diffuse gingival overgrowth.

		Biopsy Required (Yes/No)
DIGO	NO	<ul style="list-style-type: none"> - Onset 3 months after drug administration. - If the lesions are small, regression with drug withdrawal is possible. - Manifestations are dose dependent. - Synergy between drugs. - Clinical cobble stone appearance. - Inflammatory and fibrous component of lesions can vary according to the drug used.
Leukemias	NO	<ul style="list-style-type: none"> - Rapid onset in acute forms, often with first manifestation in oral cavity. - Gingival hyperplasia with spontaneous bleeding. - Early diagnosis crucial in acute forms
Lymphomas	YES (FNAC)	<ul style="list-style-type: none"> - Extremely rapid onset and the oral cavity could be sentinel of disease. - Gingival enlargement without bleeding in early stages. - Early diagnosis crucial.
Genetic	NO	<ul style="list-style-type: none"> - Slow but progressive gingival overgrowth. - Lesions particularly thick and fibrous. - Non primary inflammation. - Multidisciplinary approach to the case, if syndromic lesions suspected. - Genetic Tests.
Gingival Enlargement Induced by Hormonal Changes	NO	<ul style="list-style-type: none"> - Gingivitis gravid arum mild or intense symptoms. - During pregnancy gums appear, erythematous, edematous, and hyperplastic with hemorrhagic diathesis - Pubertal gingivitis minor symptoms compared to pregnancy. - Pubertal gingivitis characterized by hyperemic, hyperplastic, and edematous, especially in correspondence of the papillae, prone to bleeding and at risk of bacterial infections. - Gingival Acromegaly is slow but progressive development, hard consistency, and a light pink color with a predominant fibrous component. - Evaluation of GH and IGF-I laboratory test important in patients with Acromegaly.

9. Conclusions

Diffuse increases in gingival volume represent a wide range of pathological changes, with various etiological factors that make these conditions particularly heterogeneous.

The clinician plays a pivotal role in framing these patients, making a differential diagnosis, and directing them with a multidisciplinary approach towards an individualized diagnosis and a treatment.

Non-isolated HGFs are hard to classify from a diagnostic point of view as they belong to rare syndromes with clinical manifestations at times very similar to each other.

In addition to the clinician's experience, the availability of complete genetic panels that can direct patients with rare syndromes towards a diagnosis is crucial.

Not least the collaboration between different specialists in carrying out these diagnostic tests and the cooperation between them to achieve the diagnostic goal represent a key element towards an increasingly adequate and optimal management of these patients.

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