Oral Medicine

Current concepts on gingival fibromatosis-related syndromes
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Introduction

Gingival fibromatosis (GF) is a rare, benign, slowly-growing fibrous overgrowth of the gingiva. Histologically, GF is characterized by a dense accumulation and expansion of the connective tissue, with the presence of an increased number of cells, mainly fibroblasts. The overgrowth might be caused by several etiological factors, such as the administration of specific drugs (e.g., cyclosporin, nifedipine, phenytoin), the autosomal-dominant or the autosomal-recessive inheritance as an isolated feature, and/or as a syndromic manifestation. The isolated form is synonymous with idiopathic gingival overgrowth. Inflammation, leukemia, and neurofibromatosis I (von Recklinghausen disease) can also cause gingival overgrowth.\(^1\)\(^-\)\(^10\) Hereditary GF (HGF) was probably first reported by Cross in 1856, although it has been recognized for more than a century. Terms, such as elephantiasis gingivae, hereditary gingival hyperplasia, and hypertrophic gingival, have also been used. The clinical and genetic expressions of HGF are highly heterogenous, especially if presented as a manifestation of a syndrome. Usually, the isolated form is inherited in an autosomal-dominant manner while the syndromic form is characterized by an autosomal dominant, an autosomal recessive, or even an X-linked manner of inheritance.\(^6\)\(^,\)\(^9\)\(^,\)\(^10\) In the literature, the isolated form of HGF occurs with a prevalence of 1:750,000\(^3\) or 1:175,000,\(^9\) and it seems that males and females are equally affected. This review will focus on the clinical, histological, and molecular features of HGF, the more important syndromes, and the possible therapeutic aspects of the disease.

Clinical features

GF is presented as a gradually slow-growing overgrowth of the gingival tissue of the maxilla and mandible (Figure 1). It can be generalized or localized, bilaterally or unilaterally.\(^3\)\(^,\)\(^4\)\(^,\)\(^6\) Enlarged gingivae might be erythematous or normal in color, non-hemorrhagic, and asymptomatic,
and its consistency feels firm and nodular on palpation.\(^7\) The onset of overgrowth usually coincides with the eruption of permanent dentition, but it can also appear in deciduous dentition or even at birth. The localized form most often affects the labial gingiva around mandibular molars.\(^4,6,7,9\) The severity of gingival enlargement is based on the degree of overgrowth, especially when enlargement covers three-quarters or more of the crowns.\(^8\) There are many complications induced by GF, mainly functional and esthetic, such as diastemas, cross- and open bites, prolonged retention of primary dentition and delayed eruption of permanent dentition, abnormal occlusion, prominent lips, open-lip posture, and disabilities associated with eating and speech. Bacterial plaque accumulation and poor hygiene can induce periodontitis, bone resorption, and halitosis.\(^7–9\)

**Histological features**

The histological characteristics of HGF are non-specific. The connective tissue is presented as fibrous and avascular, and has densely-arranged collagen-fiber bundles running in all directions (usually types I and III), numerous fibroblasts, and mild chronic inflammatory cells.\(^1–3,5,6,8–10\) The overlying epithelium is squamous, hyperplastic, acanthotic, and parakeratinized with thin, elongated rete ridges in the connective tissue.\(^1,2,5\) Fibroblasts are flat or star shaped, with slender cytoplasmic processes, irregular nuclei, and a well-developed Golgi apparatus.\(^7\) Some unusual findings, such as small, calcified particles; amyloid deposits; odontogenic epithelial islands, osseous metaplasia in the connective tissue, and ulceration of the mucosa might also be present.\(^1,2,5,9\) In the literature, there are reports of the distribution of myofibroblasts, with the exception of fibroblasts in the connective tissue of the fibrotic gingiva.\(^10\)

**Pathogenesis**

As mentioned earlier, HGF as an isolated trait is transmitted in an autosomal-dominant pattern, while the syndromic form is transmitted in an autosomal-dominant or an autosomal-recessive manner, or as even an X-linked inheritance. Many patients who develop a certain syndrome have consanguineous parents. There is a wide spectrum of clinical and genetic heterogeneity, and patients who are members of the same family can exhibit different phenotypes as a result of a variable penetrance of HGF.\(^9–17\) As suggested, chromosomes 2, 4, and 5 seem to include the most important and known genetic loci, including 2p21-p22, 2p13-p16, 5q13-q22, 4q21, and 4q that enable mutations, duplications, deletions, and other genetic anomalies to take place. Other genetic loci, such as 8, 14q, 19p, 19q, and Xq, are also related to syndromes associated with HGF. Recent findings have been reported that a mutation in Son of sevenless-1 (SOS-1) is the most frequent genetic mechanism related to the isolated form of HGF.\(^1,8,9,15\) SOS-1 is a bifunctional guanine nucleotide factor that regulates the activity of Ras, Rac, and Rho proteins. The function of this protein net is responsible for cell differentiation and proliferation, and is also thought to play a key role in cancer pathogenesis and cell accumulation seen in HGF. The specific mutation is localized in three genetic loci: two maps to chromosome 2 (GINGF1 2P21-22 and GINFG3 2p22.3-p23.3), which do not overlap, and one map to chromosome 5 (GINGF2 5q13-q22).\(^3,7,9,10\)

The biochemical mechanisms involved are still unknown. It seems that the fibroblast proliferation rate is higher in HGF fibroblasts compared to normal gingiva. Several analyses have also revealed a higher percentage of these cells in the G\(_2\)/M and S phases of the cell cycle. C-myc proto-oncogene expression has been demonstrated to specifically induce the increased proliferation of HGF fibroblasts, while these highly-proliferative cells produce elevated levels of fatty acid synthase and the androgen receptor. Furthermore, testosterone induces the production of interleukin-6 by HGF fibroblasts. The relationship between sex hormones, gingival overgrowth, and fibroblast proliferation is obvious.\(^1,9\)

The accumulation of collagen and fibronectin in the extracellular matrix (ECM) is caused by the lack of balance between metalloproteinases and their inhibitors (tissue inhibitors of metalloproteinases), as well as the decreased degradation of ECM due to a genetic defect. As a result, a gradual accumulation of collagen types I and II is observed in gingival tissues. Finally, impaired collagen
phagocytosis was proposed as a possible mechanism of fibrosis.\textsuperscript{7,9}

Syndromes

GF is a relatively rare condition that can occur at any age, although it is most common in younger patients.\textsuperscript{18} The inherited condition in which the gingival tissue spontaneously and progressively enlarges is identified as HGF. The condition can occur as an isolated disease affecting only gingivae, or as a part of a syndrome or chromosomal abnormality; both autosomal-dominant and autosomal-recessive forms of this disorder have been described.\textsuperscript{7,9} The syndromes associated with GF and the clinical features are presented in Table 1. The mode of inheritance is believed to be autosomal dominant, although reports of a recessive mode of inheritance have also been published.\textsuperscript{19} The isolated form of HGF might result from a single gene mutation, and the syndromic forms might result from alterations of multiple genes or a gene dosage effect.\textsuperscript{4,20} The gingival enlargement usually begins at the time of eruption of the permanent dentition, but can develop with the eruption of the primary dentition. It is rarely present at birth.\textsuperscript{20}

HGF, as a part of a syndrome and not as an idiopathic form, is related to hypertrichosis and/or mental retardation syndrome. Linkage studies have localized loci for isolated, non-syndromic autosomal-dominant forms of GF to chromosomes 2p21-p22 and 5q-13-q22 (Mendelian Inheritance in Man 135300).\textsuperscript{20} Similar studies have localized loci for GF combined with mental retardation to chromosome 2p13-p21. The coexistence of GF and mental retardation does not comprise a distinct syndrome, but provides direct evidence of genetic heterogeneity for HGF.\textsuperscript{6}

Because of the syndrome’s overlapping, due to genetic heterogeneity, there are few references in the worldwide literature that combine two or more syndromes. In a case report, HGF, generalized hypertrichosis, mental retardation, and epilepsy are considered to resemble to Zimmermann–Laband, Ramon, and Cantu syndromes.\textsuperscript{12}

The coexistence of gingival hypertrophy, hypertrichosis, mental retardation, and brachymetacarpia in two sisters is another example of syndrome overlapping (Rutherford, Cross, Ramon, Zimmermann–Laband).\textsuperscript{15}

The coexistence of HGF with periodontal lesions has been described in case reports. In two studies, an individual presented with HGF and generalized aggressive periodontitis.\textsuperscript{1,21} Diagnosis was based on clinical, radiographic, histopathological, and immunological assessments. However, further research is needed to establish a syndromic association between the two conditions based on genetic evaluation and linkage studies.\textsuperscript{1}

Differential diagnosis

The diagnosis is based on the patient’s medical and family history, the clinical presentation, the pattern of recurrence, and the characteristic microscopic features of the histology samples.\textsuperscript{19} There are currently no specific immunohistochemical markers available for the disease.\textsuperscript{7} Thus, elements from the medical history indicate or exclude the implication of drugs responsible for GF (antiseizure drugs, antihypertensives, immunosuppressives). Laboratory and clinical examinations and microscopic findings indicate or eliminate gingival enlargement as part of leukemia or the presence of an acute or chronic dento-alveolar abscess. Chronic periodontitis consists an inflammatory disease of the gingival tissues, and the differential diagnosis to GF depends on the former’s response to antibiotics,\textsuperscript{22} bleeding tendency on pressure, and the different microscopic characteristics.

The detection of specific mutations, including duplications, deletions, and/or other anomalies of chromosomes, documents the association of HGF or other syndromes. The characteristics most often associated with HGF are hypertrichosis, mental retardation, and epilepsy.\textsuperscript{4,20,23}

Family history and clinical examination constitute important tools for the differential diagnosis of HGF and peripheral ossifying fibroma, where spherical and laminated calcified structures, resembling dysplastic enamel or cementsicles, and nests of epithelia, resembling odontogenic epithelial rests, are observed in HGF microscopic samples.\textsuperscript{10}

Treatment

The treatment of GF consists of surgical excision of the hyperplastic tissue to restore the gingival contours, external or internal bevel gingivectomy in association with gingivoplasty, an apically-positioned flap, electrosurgery, and carbon dioxide laser.\textsuperscript{10,23} Although there is general consensus on the modality of treatment for GF patients, there are controversies as to the exact period in which it should be accomplished. According to several authors, the best time is when all of the permanent dentition has erupted, because the risk of recurrence is greater before eruption. However in some cases, a delay in the surgical treatment might cause significant consequences for the patient, such as primary dentition retention with delay in the eruption of the permanent teeth, difficulties in mastication and phonation, malpositioning of teeth, aesthetic effects, and psychological problems for the patients and relatives. Treatment depends on the severity of enlargement and shows varying degrees of success. When the enlargement is minimal, thorough scaling of teeth and home care might be all that is required to maintain good appearance. The treatment of HGF patients is conservative, although
<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Inheritance</th>
<th>OMIM category no.</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>GF with hypertrichosis16,26</td>
<td>AD</td>
<td>135400</td>
<td>GF, hypertrichosis, mental retardation, muscular hypotonia</td>
</tr>
<tr>
<td>Congenital generalized hypertrichosis6</td>
<td>X-linked</td>
<td>307150</td>
<td>Hypertrichosis Affected females have asymmetric, patchy hirsutism</td>
</tr>
<tr>
<td>Gingival fibromatosis with distinctive facies6</td>
<td>AR</td>
<td>228560</td>
<td>GF, hypertrichosis, mental retardation, muscular hypotonia, down-slanted palpebral fissures, flat nasal bridge, hypoplastic nares, cupid-bow mouth, high arched palate</td>
</tr>
<tr>
<td>Jones syndrome–GF with progressive deafness5</td>
<td>AD</td>
<td>135500</td>
<td>GF, hypertrichosis, mental retardation, muscular hypotonia, down-slanted palpebral fissures, flat nasal bridge, hypoplastic nares, cupid-bow mouth, high arched palate</td>
</tr>
<tr>
<td>Zimmermann–Laband syndrome27–29</td>
<td>AR</td>
<td>228600</td>
<td>Multiple fibroblastic tumors involving skin, striated muscles, bones, and viscera</td>
</tr>
<tr>
<td>Ramon syndrome6,30</td>
<td>AR</td>
<td>266270</td>
<td>GF, multilocalized tumors involving skin, striated muscles, bones, and viscera</td>
</tr>
<tr>
<td>Congenital generalized fibromatosis16,31</td>
<td>AR</td>
<td>228550</td>
<td>Multiple fibroblastic tumors involving skin, striated muscles, bones, and viscera</td>
</tr>
<tr>
<td>Juvenile hyaline fibromatosis (Murray Puretic–Drescher)6,16,32,33</td>
<td>AR</td>
<td>228600</td>
<td>GF, multiple subcutaneous tumors, sclerodermaform atrophy, osteolytic and osteoclastic skeletal lesions, recurrent suppurrative infections, painful flexural joint contractures, osteolyis of terminal phalanges, stunted growth/early death</td>
</tr>
<tr>
<td>Systemic infantile hyalinosis6,16</td>
<td>AR</td>
<td>236490</td>
<td>Gingival hypertrophy, thickened skin/focal skin nodularity, joint contractures/osteoporosis, diarrhea/failure to thrive, recurrent infections/death (infancy)</td>
</tr>
<tr>
<td>Rutherford syndrome–gingival hypertrophy with corneal dystrophy6,16</td>
<td>AR</td>
<td>180900</td>
<td>Gingival hypertrophy, corneal opacity, mental retardation, failure of tooth eruption, aggressive behavior</td>
</tr>
<tr>
<td>Cross syndrome5,16</td>
<td>AR</td>
<td>257800</td>
<td>Hypopigmenation/silver grey hair color, microphthalmia with cloudy cornea, mental retardation/spasticity, athetoid movements/growth retardation</td>
</tr>
<tr>
<td>Prune belly9</td>
<td>Unclear</td>
<td>264140</td>
<td>Absence of abdominal muscles, abnormalities of urinary tract, cryptorchidism, facial dimorphism</td>
</tr>
<tr>
<td>Gangliosidosis6,16</td>
<td>X-linked</td>
<td>305650</td>
<td>Gingival hypertrophy, macroglossia, coarse face/micrognathia, loose skin/inguinal hernia, delayed growth/development of musculoskeletal system, neonatal hypotonia, delayed motor development</td>
</tr>
<tr>
<td>Borrone dermato-cardio-skeletal syndrome6,16,34</td>
<td>AR, X-linked</td>
<td>211170</td>
<td>Gingival hypertrophy/coarse face, late eruption of teeth/lips of teeth, thick skin/acin conglobata, osteolysis/large joint flexion contractures, short stature/brachydactyly/congenital heart failure, inguinal hernia</td>
</tr>
<tr>
<td>Mannosidosis4,6,16</td>
<td>AR</td>
<td>248500</td>
<td>Gingival hypertrophy/macroglossia, coarse features/prognathism, thick eyebrows/low anterior hairline, deafness/flexibility of joints, hepatosplenomegaly, recurrent respiratory tract infections, muscular hypotonia/mental retardation</td>
</tr>
<tr>
<td>Costello syndrome7,35</td>
<td>AD</td>
<td>218040</td>
<td>Characteristic faces, distinctive hand posture and appearance, severe feeding difficulty, failure to thrive, congenital heart disease, atrial arrhythmia, cardiomyopathy, autistic behaviors, short stature increased risk of malignancy (rhabdomyosarcoma)</td>
</tr>
<tr>
<td>I-cell disease (mucolipidosis)13</td>
<td>AR</td>
<td>607014</td>
<td>Coarse facial features, normal head circumference relative to body size, puffy eyelids with slight exophthalmia, excessve prominence of the epicantlic folds, depressed nasal bridge, full cheeks exhibiting multiple fine telangiectasias, incompetent lips, gingival and alveolar enlargement with buried teeth, thick tongue</td>
</tr>
<tr>
<td>Donohue syndrome–leprechaunism13</td>
<td>AR</td>
<td>246200</td>
<td>Hirsutism, acanthosis nigricans, large mouth, thick lips, gingival hypertrophy, paucity of lymphatic tissue, hepatic cholestasis, and fibrosis, large hands, feet, retarded bone age, reduced muscle mass, distended abdomen</td>
</tr>
<tr>
<td>Ectro-amelia7</td>
<td>Unclear</td>
<td>183600</td>
<td>Split hand/foot malformation</td>
</tr>
</tbody>
</table>
extraction of the dentition and reduction of the alveolar bone have been recommended in the past. The patients receive a conservative treatment that consists of quadrant-by-quadrant internal bevel gingivectomy in association with gingivoplasty, followed by 0.12% chlorhexidine oral rinse twice a day for 2 weeks after each surgery. The interval between surgeries is 2–3 months. Although recurrence is unpredictable, it is most often seen in children and teenagers, rather than adults. It has been demonstrated that recurrence is faster in areas with dental plaque accumulation. Normally recurrence is minimal or delayed if good oral hygiene is achieved by a combination of monthly examinations with professional cleaning and oral hygiene instructions.

The advantages of CO₂ laser in comparison to the conservative or surgical methods consist of limitations in bleeding, pain, and treatment duration, as well as allowing treatment of all quadrants in one visit with minimal discomfort, which is an important consideration in children’s therapy.

Myofibroblasts, the main cell type associated with interstitial fibrosis, might be implicated with the gingival overgrowth observed in HGF patients. Recently, it has been documented that GF cell cultures are characterized by the increased production of transforming growth factor β-1 (TGF-β1), and it was demonstrated that TGF-β1 induces gingival–myofibroblast transdifferentiation in GF. Consequently, the suppression attempt of TGF-β1 could become a future treatment aim. Moreover, recent research findings establish that γ-interferon (IFN-γ) might be clinically effective in attenuating excessive accumulation of the ECM produced by myofibroblasts, and thus it can be proposed that IFN-γ might be useful in preventing the gingival overgrowth in HGF.

In conclusion, GF causes aesthetic, functional, and psychological problems in a patient’s life whenever it appears in any of its clinical forms (drug associated, leukemic, idiopathic, and syndromic). Gingival overgrowth as a clinical characteristic of idiopathic GF is compatible with life, but the related dental complications worsen patients’ adaptation in daily emotional, social, and functional requirements.

GF can be one feature of several multisystem syndromes, occasionally associated with severe medical problems, and has a variety of psychosocial consequences for individuals. The coexistence of GF with other clinical characteristics could be evaluated as a new syndrome in the near future.

**References**


**Table 1.** (Continued)

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Inheritance</th>
<th>OMIM category no.</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cantu syndrome⁴⁶</td>
<td>Unclear/possibly AR 23985</td>
<td></td>
<td>Congenital hypertrichosis, osteochondrodysplasia, cardiomegaly, mental retardation, macrocephaly, enlarged sella turcica, prominent mouth, narrow shoulders-thorax, broad ribs, platyspondyly and coxa valga</td>
</tr>
<tr>
<td>Amelogenesis imperfecta¹⁰</td>
<td>AD/X-linked</td>
<td>130900, 104500, 204650</td>
<td>Deficiency in enamel formation, defects in the mineral and protein contents, unerupted teeth, pulpal calcifications, root and crown resorptions, hypercementosis, taurodontism, GF</td>
</tr>
<tr>
<td>Schinzel–Giedion syndrome⁸</td>
<td>–</td>
<td>269150</td>
<td>Multiple skull anomalies, congenital heart defect, hydronephrosis, club feet</td>
</tr>
<tr>
<td>Sweet-like syndrome⁶,³⁷</td>
<td>–</td>
<td>–</td>
<td>Fever, neutrophilia, cutaneous lesions/plaques, nodules, GF</td>
</tr>
</tbody>
</table>

AD, autosomal dominant; AR, autosomal recessive; GF, gingival fibromatosis; OMIM, Online Mendelian Inheritance in Man catalogue number.


