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REVIEW ARTICLE

Oral Medicine

Current concepts on gingival fibromatosis-related syndromes

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Abstract

Gingival fibromatosis is a rare, benign, slowly-growing fibrous overgrowth of the gingiva, with great genetic and clinical heterogeneity. Gingival fibromatosis/overgrowth can be inherited as an isolated trait (hereditary gingival fibromatosis) and/or as a component of a syndrome, or it can be drug induced. As a clinical manifestation of a syndrome, gingival fibromatosis is usually associated with generalized hypertrichosis, mental retardation, or epilepsy. Gingival fibromatosis and its related syndromes are mainly inherited in an autosomal-dominant manner, but autosomal-recessive inheritance has also been reported. Clinical syndromic presentation includes Zimmermann–Laband syndrome, Ramon syndrome, Rutherford syndrome, Cowden syndrome, Cross syndrome, Göhlich–Ratmann syndrome, Avani syndrome, and I-cell disease. However, a phenotypic overlap has been suggested, as many combinations of their systemic manifestations have been reported. Treatment of choice is usually gingivectomy with gingivoplasty. Before any therapy, clinical practitioners must take into consideration the clinical course of a particular syndrome and every possible functional and esthetic disorder.

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 1:1 750 000[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,

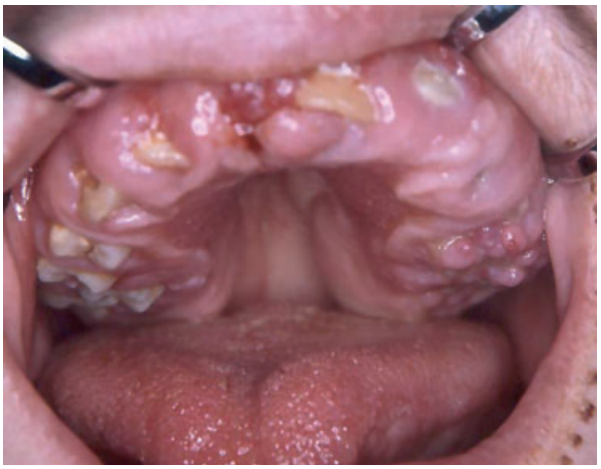

Figure 1. Gingival fibromatosis is presented as a gradually slow-growing overgrowth of the gingival tissue of the maxilla and mandible.

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.[2] 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.[7–9]

Syndromes

GF is a relatively rare condition that can occur at any age, although it is most common in younger patients.[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.[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.[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.[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.[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).[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.[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.[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).[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.[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.[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.[19] There are currently no specific immunohistochemical markers available for the disease.[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,[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.[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 cementicles, and nests of epithelia, resembling odontogenic epithelial rests, are observed in HGF microscopic samples.[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.[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 1. Syndromes associated with gingival fibromatosis

Syndrome	Inheritance	OMIM category no.	Features
GF with hypertrichosis[16,26]	AD	135400	GF, hypertrichosis, mental retardation, muscular hypotonia
Congenital generalized hypertrichosis[6]	X-linked AD/AR	307150	Hypertrichosis Affected females have asymmetric, patchy hirsutism
Gingival fibromatosis with distinctive facies[6]	AR	228560	GF, macrocephaly, bushy eyebrows, synophrys, hypertelorism, down-slanted palpebral fissures, flat nasal bridge, hypoplastic nares, cupid-bow mouth, high arched palate
Jones syndrome–GF with progressive deafness[6]	AD	135550	GF, progressive sensor, neural hearing loss
Zimmermann–Laband syndrome[27–29]	–	135500	GF–hypertrophy, absence/dysplasia of the terminal phalanxes or nails of the hands or feet and thick lips, bulbous soft nose, thick floppy ears, mental retardation, hepatosplenomegaly, hypertrichosis, hyperextensibility of the joints, ocular symptoms
Ramon syndrome[6,30]	AR	266270	GF, cherubism, seizures, mental deficiency, hypertrichosis, stunted growth, juvenile rheumatoid arthritis
Congenital generalized fibromatosis[16,31]	AR	228550	Multiple fibroblastic tumors involving skin, striated muscles, bones, and viscera
Juvenile hyaline fibromatosis (Murray Puretic–Drescher)[6,16,32,33]	AR	228600	GF, multiple subcutaneous tumors, sclerodermiform atrophy, osteolytic and osteoclastic skeletal lesions, recurrent suppurative infections, painful flexural joint contractures, osteolysis of terminal phalanges, stunted growth/early death
Systemic infantile hyalinosis[6,16]	AR	236490	Gingival hypertrophy, thickened skin/focal skin nodularity, joint contractures/osteoporosis, diarrhea/failure to thrive, recurrent infections/death (infancy)
Rutherford syndrome–gingival hypertrophy with corneal dystrophy[6,16]	AD	180900	Gingival hypertrophy, corneal opacity, mental retardation, failure of tooth eruption, aggressive behavior
Cross syndrome[9,16]	AR	257800	Hypopigmenation/silver grey hair color, microphthalmia with cloudy corneas, mental retardation/spasticity, athetoid movements/ growth retardation
Prune belly[9]	Unclear	264140	Absence of abdominal muscles, abnormalities of urinary tract, cryptorchidism, facial dimorphism
Gangliosidosis[6,16]	X-linked	305650	Gingival hypertrophy, macroglossia, coarse face/micrognathia, loose skin/inguinal hernia, delayed growth/hepatosplenomegaly, neonatal hypotonia, delayed motor development
Borrone dermato-cardio-skeletal syndrome[6,16,34]	AR, X-linked	211170	Gingival hypertrophy/coarse face, late eruption of teeth/loss of teeth, thick skin/acne conglobata, osteolysis/large joint flexion contractures, short stature/brachydactyly/congestive heart failure, inguinal hernia
Mannosidosis[4,6,16]	AR	248500	Gingival hypertrophy/macroglossia, coarse features/prognathism, thick eyebrows/low anterior hairline, deafness/lens opacities, hepatosplenomegaly, recurrent respiratory tract infections, muscular hypotonia/mental retardation
Costello syndrome[7,35]	AD	218040	Characteristic faces, distinctive hand posture and appearance, severe feeding difficulty, failure to thrive, congenital heart disease, atrial arrhythmia, cardiomyopathia, autistic behaviors, short stature increased risk of malignancy (rhabdomyosarcoma)
I-cell disease (mucolipidosis)[13]	AR	607014	Coarse facial features, normal head circumference relative to body size, puffy eyelids with slight exophthalmia, excessive prominence of the epicanthic folds, depressed nasal bridge, full cheeks exhibiting multiple fine telangiectasia, incompetent lips, gingival and alveolar enlargement with buried teeth, thick tongue
Donohue syndrome–leprechaunism[13]	AR	246200	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
Ectro-amelia[7]	Unclear	183600	Split hand/foot malformation

Table 1. (*Continued*)

Syndrome	Inheritance	OMIM category no.	Features
Cantu syndrome[36]	Unclear/possibly AR	23985	Congenital hypertrichosis, osteochondrodysplasia, cardiomegaly, mental retardation, macrocephaly, enlarged sella turcica, prominent mouth, narrow shoulders-thorax, broad ribs, platyspondyly and coxa valga
Amelogenesis imperfecta[10]	AD/X-linked	130900, 104500, 204650	Deficiency in enamel formation, defects in the mineral and protein contents, unerupted teeth, pulpal calcifications, root and crown resorptions, hypercementosis, taurodontism, GF
Schinzel–Giedion syndrome[8]	–	269150	Multiple skull anomalies, congenital heart defect, hydronephrosis, club feet
Sweet-like syndrome[8,37]	–	–	Fever, neutrophilia, cutaneous lesions/plaques, nodules, GF

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

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.[24] 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.[9,10,19,23]

The advantages of CO_2 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.[18]

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.[25] 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.[25]

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.

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