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Review Article

The Multiple Obscure Findings of Gingival Fibromatosis: A Review

Zeba Rahman Siddiqui*, Akanksha Singh, Siya Kumari, Srashti

Department of Periodontology, Career Post Graduate Institute of Dental Sciences and Hospital, Lucknow, Uttar Pradesh, India

ABSTRACT

Gingival Fibromatosis (GF) is a slowly progressive, benign and rare disorder characterized by diffuse or local fibrous growth of gingiva. Hereditary Gingival Fibromatosis (HGF), which is usually an autosomal dominant trait, is the most common form. The attached gingiva, marginal gingiva and the interdental papilla is affected. In severe condition functional, periodontal, aesthetic and psychological problems may occur. Histopathology shows epithelial acanthosis and atypically abundant inflammatory infiltrates distributed in the sub-epithelial and connective tissue. The pathophysiology of gingival fibromatosis comprises excessive accumulation of extracellular matrix proteins. Mutation in the Son-of-Sevenless-1 (SOS-1) gene has been suggested as genetic attribute of hereditary gingival fibromatosis. To stabilize the long-term outcomes and alleviate suffering of adversely affected, non-surgical therapies and oral hygiene maintenance are important.

Keywords: Gingival fibromatosis; Hereditary gingival fibromatosis; Pathophysiology; Genetic attributes; Histopathology

INTRODUCTION

Gingival fibromatosis is a slowly progressive benign enlargement of the oral gingival tissues which may seem as an isolated entity or to a certain extent as a genetic disease or syndrome, as Drug-Induced Gingival Overgrowth (DIGO) or as Idiopathic Gingival Fibromatosis (IGF) [1].

Hereditary Gingival Fibromatosis (HGF), which is usually an autosomal dominant trait, is the most common form. It is a rare genetic disorder characterized by a non-haemorrhagic, benign, and fibrous gingival overgrowth that came out in isolation or as part of a syndrome. In the classification by Armitage, HGF is a gingival lesion of genetic origin [2].

Here, we emphasize on the gingival fibromatosis and an updated review of the clinical features, differential diagnosis, aetiology, pathophysiology and management of GF.

Epidemiology

GF correlated with hereditary factors (non-syndromic): HGF is a disease with unknown prevalence.

GF correlated with genetic diseases and syndromes: GF with craniofacial dysmorphism, GF with progressive deafness, amelogenesis imperfecta, Nephrocalcinosis syndrome, Zimmermann-Laband syndrome, Juvenile hyaline fibromatosis and Rutherfurd syndrome occur with a prevalence of one per million populations.

Drug induced inflammatory enlargement: The anti-epileptic drug e.g., phenytoin has 70% incidence rate. In patients treated with nifedipine prevalence is estimated around 15%-83%, and 8% and 70% with Cyclosporine A (CsA).

Idiopathic gingival enlargement: Out of 750,000 individuals at least 1 are affected by IGF, and can be seen in male or female and in either of the jaws.

CLINICAL DIAGNOSIS

Periodontal examination, clinical examinations, medical history and family history made up a diagnosis. These aspects decide whether disease is inherited or acquired, Histopathological analysis shows the epithelial acanthosis, dense connective tissue, cellular content inflammatory infiltrates and the extent of fibrosis. Radiographs serve mainly to diagnose the type and severity of gingival involvement, and bone loss [3].

CLINICAL IMPLICATIONS

Clinical features

It is benign, non-haemorrhagic and slowly progressive gingival hyperplasia.

The marginal gingiva, attached gingiva and the interdental papilla

Correspondence to: Zeba Rahman Siddiqui, Department of Periodontology, Career Post Graduate Institute of Dental Sciences and Hospital, Lucknow, Uttar Pradesh, India, Tel: +91-9628404498; E-mail: zeba.rahman1@gmail.com.

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is affected, although it does not extend beyond the Muco-Gingival Junction (MGJ). GF may also appear as a localised lesion. The gingival overgrowth covers part of or the entire crown, resulting in diastemas, retention of primary teeth, teeth displacement, and sometimes can cause masticatory, phonetic, psychological, and aesthetic problems (Figure 1) [4].

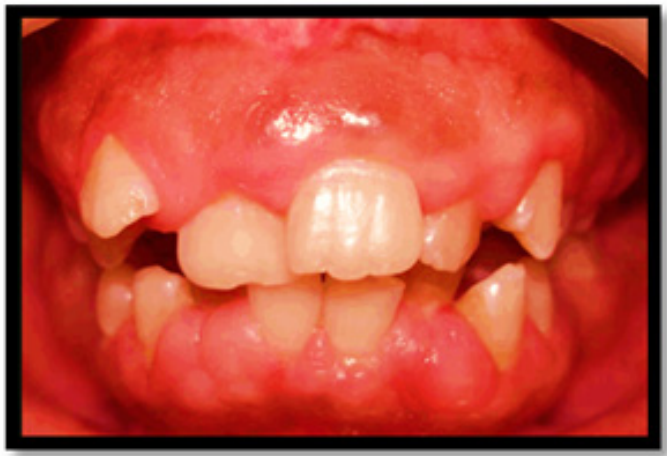

Figure 1: Gingival fibromatosis affecting both arches.

Gingival hyperplasia usually presents a normal coloration or can be erythematous, and composed of dense fibrous tissue. On palpation it feels like firm and nodular. Although the alveolar bone is usually unaffected, gingival overgrowth leads to pseudo pocketing and periodontal problems, because of poor oral hygiene. HGF may result as an expansion of interdental gingiva, suggesting that interdental papilla is predisposed to overgrowth [5].

HISTOLOGICAL ATTRIBUTES

The typical histopathology involves hyperplasia of the epithelium with elongated rete ridges spreading into the underlying connective tissue (Figure 2). The connective tissue contains excess collagen, with relatively few fibroblasts and blood vessels [6]. Enlarged fibroblasts interspersed with thin and thick collagen fibrils. Elastic and oxytalan fibres are commonly seen in lesions [7]. Rarely, small osseous calcifications and abundant neurovascular bundles may also be present. Plaque accumulation and pseudo pockets formation results in inflammatory infiltration of the connective tissue [8,9].

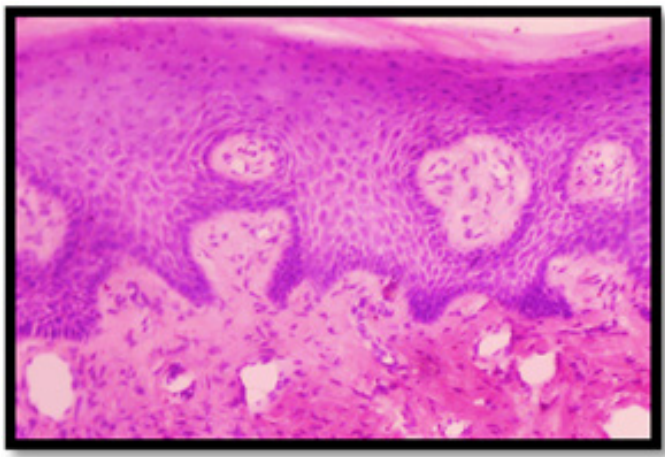

Figure 2: Haematoxylin and eosin staining shows epithelial acanthosis and atypically abundant inflammatory infiltrates distributed in the sub-epithelial and connective tissue, original magnific.

PATHOGENESIS AND PATHOPHYSIOLOGY

The pathologic manifestation of GF is excessive accumulation of ECM proteins, including collagen type I.

Cell proliferation

It is not clear whether increased cell proliferation contributes to HGF. Histologically, HGF shows reduced fibroblast density, and there is no increase in the expression of the proliferation markers PCNA or Ki-67 in fibroblasts as compared with normal tissue [10,11]. In contrast, fibroblasts from HGF appear to proliferate faster than normal cells in culture [12,13]. The increased proliferation rate of HGF fibroblasts was associated with increased Fatty Acid Synthase (FAS) expression, and the inhibition of FAS reduced proliferation rates to normal levels [14]. C-myc is a nuclear proto-oncogene that is expressed by proliferating cells, and its increased expression has been associated with deregulated cell growth [15]. Increased proliferation of HGF fibroblasts was also linked to autogenous Transforming Growth Factor- (TGF-), since neutralizing antibodies to TGF-1 reduced proliferation of HGF fibroblasts [16]. Epidermal Growth Factor (EGF) and its receptor (EGFR) are important regulators of epithelial cell proliferation [17].

Expression of transforming growth factor and its receptors

In HGF, there is a significant proportional increase in fibroblasts expressing TGF-1 and TGF-3, while the proportion of cells expressing TGF-2 is decreased as compared with healthy tissue. In addition, the proportions of TGF-RI/II-positive cells are significantly increased in HGF [10]. Cell culture experiments have also indicated that HGF fibroblasts produce increased levels of TGF-1 and TGF-2, which results in increased ECM deposition by an autocrine mechanism specific to HGF fibroblasts [11-13].

Extracellular matrix production and degradation

ECM is an important regulator of cell functions as well as provides mechanical support. Furthermore, ECM molecules serve as storage for various growth factors and participate in the regulation of their activation [18]. Thus, altered abundance or composition of ECM may play an active part in the pathogenesis of HGF. The hallmark of HGF is the accumulation of excess ECM. Accordingly, production of type I collagen along with heat-shock protein 47 (Hsp47, a molecular chaperone involved in collagen secretion), glycosaminoglycan, and fibronectin is increased in cultured HGF fibroblasts [11-13]. TGF- can promote ECM accumulation by increasing ECM synthesis. It can also inhibit ECM breakdown by down-regulating, Matrix Metalloproteinase (MMP) expression, and by increasing expression of Tissue Inhibitors of Matrix Metalloproteinases (TIMP).

TIMPs inhibit MMP activity, and a high ratio of TIMPs to MMPs results in excess collagen accumulation. Exogenous or autocrine TGF-1 up-regulates type I collagen and down-regulates MMP-1 (the major collagenase in fibroblasts) expression in gingival fibroblasts [19]. Thus, it is possible that fibroblasts in HGF, inherently or as a response to elevated TGF- activity, produce less MMPs and more ECM proteins as compared with normal cells, resulting in ECM accumulation. Interestingly, HGF may also involve altered cross-linking of collagen, resulting in increased resistance to degradation. The ECM molecule decorin potently blocks collagen phagocytosis, collagen internalization and lysosomal degradation by gingival

fibroblasts mediated by an endocytic process that involves the cell-surface receptor Endo180 (also called CD280 or urokinase plasminogen activator receptor-associated protein, uPARAP) [5].

GENETIC ATTRIBUTES

Identification of the genetic mutations, uncover targets involved in HGF can aids for disease diagnosis and novel treatment modalities. It will also provide better understanding of the molecular mechanisms of HGF and other fibrotic processes. Studies have pointed mutations in chromosome-2 as a possible cause of HGF. Originally, the region of 2p13-p21 in chromosome-2 was associated with a syndromic form of HGF. The affected locus was later refined to encompass the region 2p13-2p16 [20]. In the Brazilian family, the HGF1 locus was confined to a candidate interval, and sequencing of the 16 genes found in this region revealed a mutation in a gene that codes for a guanine nucleotide exchange factor, Son-of-Sevenless-1 (SOS-1) [21]. Furthermore, the SOS-1 locus was likely not affected in the Chinese families, suggesting a different genetic background [21,22]. Thus, HGF is considered genetically heterogenous involving several genes. Remarkably, a different form of HGF shows relatively similar histological outcomes, suggesting that the genetic mutations affect different levels cellular or molecular pathways. The mutation in SOS-1 will allow researchers to uncover some of the signalling mechanisms in HGF.

GENETIC COUNSELLING

HGF is an autosomal-dominant or less commonly autosomal-recessive mode of inheritance. Autosomal dominant forms are isolated (non-syndromic) and have been associated genetically to several loci.

- Family members are called to clinic to confirm the presence of HGF, after clinical/periodontal examination, family history and laboratory tests indicate a genetic background.
- Draw a pedigree diagram, to determine whether it account for a confined entity or synchronize with other disease or syndrome.
- The patient is kept in the supervision of a geneticist for additional clinical examination and specialized diagnostic tests when systemic disease or syndrome is suspected [8].

MANAGEMENT

The patient's clinical findings, medical examination influence the patient's management.

Non-surgical approach

Non-surgical treatment includes scaling and root planning, oral hygiene instructions with use of chlorhexidine mouth rinses.

Administration of antibiotics, such as amoxicillin and metronidazole, along with anti-inflammatory (ibuprofen) and analgesic (paracetamol) drugs are prescribed [23].

Surgical approach

The treatment modality of GF includes external bevel gingivectomy. If complicated by bony defects, a flap surgery is carried out. Hypertrophic tissue can be also being removed by electrosurgery or by laser, which reduce the risk of bleeding and pain. Use of laser excision, reportedly reduce the recurrence, re-growth of the excised gingival tissue, decreases significantly the quantity of local anaesthetic used, leads to better visibility, reduce chairside time, and results in better patient compliance. Management also includes non-surgical treatments, surgery with regenerative or resective osseous therapy and anti-microbial treatment. Bone grafts, barrier membranes, wound healing agents and enamel matrix protein can be used as regenerative techniques. Full mouth disinfection, local drug delivery and host immune response modulation are other choice of treatment.

Therefore, to stabilize the long-term outcomes and alleviate suffering of adversely affected, non-surgical therapies to treat GO are of great importance [24].

DIRECTIONS FOR FUTURE RESEARCH

It will be important to acquire more information and to study about the specific gene mutations in various forms of HGF. Modulation of the expression of target genes in cells and animals will act as an additional tool for researching on the importance of the target pathways in HGF. HGF (non-syndromic) manifests only in gingiva, although other tissues do not show any fibrosis. The signalling pathways which induce non syndromic form of HGF are regulated within the gingival cells. Therefore, it will be important to study the key pathways in more detail, specifically in gingival cells. Previously, studies about HGF have focused mainly on connective tissue cells, interaction between epithelium and fibroblasts [18]. Now, more studies on the role of the epithelial-mesenchymal interactions in HGF are required.

DISCUSSION AND CONCLUSION

GF is genetically heterogenous disorder clinically seen as firm, painless enlargement of gingiva. Pathogenesis, aetiology of GF is distinguished from other gingival overgrowth through a differential diagnosis which includes consideration of all pathologies in the oral cavity with excessive accumulation of gingival tissue, including syndromic HGF.

ECM components, particularly collagen type I, are the main pathologic manifestation of all types of GF; however, the molecular mechanisms remain undefined.

Newer studies in regards to, the innate and acquired immune response, growth factors, and gingival epithelial and connective tissue cells, and cytokines are required for a better knowledge of the molecular and mechanistic pathways of gingival connective tissue. Better disease management and less invasive therapeutic methods should be implemented into daily dental practice.

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