CASE REPORT

Generalised fibrotic gingival enlargement in a psoriatic patient: an association or a coincidence?

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SUMMARY

Gingival fibromatosis is a rare, benign, slow progressive fibrous overgrowth of gingiva, with great genetic and clinical heterogeneity. It can be inherited as an isolated trait (hereditary/idiopathic gingival fibromatosis), and/or as a component of a syndrome. We report a case of a young girl suffering from psoriasis who also presented with an unusual generalised idiopathic gingival fibromatosis. Psoriasis, a chronic inflammatory skin disease, of multifactorial origin, is characterised by keratinocyte hyperproliferation, dedifferentiation, neoangiogenesis and inflammation. T cell-mediated immunity is considered to be the key element in the disease process. The existence of oral mucosal alterations in patients with psoriasis is a controversial topic, as histopathological correlations are not clearly evident, and oral and cutaneous lesions do not follow a parallel course. However, this article highlights a possible association of T-lymphocyte stimulation inducing fibroblasts to undergo epidermal hyperproliferation and increased collagen production in the gingiva, which in turn may be responsible for inducing gingival hyperplasia.

extensive lesions on the trunk, scalp, extremities and nails, and had stiffened and deformed knees and finger joints. Treatment history included ayurvedic and allopathic treatment alternately for 6 years. The allopathic treatment included weekly intralesional steroidal injections in a tapering dose (triamcinolone acetonide starting dose was 10 mg/mL), and antihistamine (diphenhydramine, 25 mg three times per day), methotrexate (2.5 mg) and acitretin (25 mg) for 2–4 weeks during periods of exacerbation. She was not on any immunosuppressants or drugs reported to induce gingival enlargement. She had undergone narrow band ultraviolet type B phototherapy and was using joint splints for her joint deformities. At presentation to our clinic, she had discontinued allopathic medication for over a month. Her family history was unremarkable. Consanguinity of marriage in the family was not reported.

On general examination, red, raised and scaly lesions with no pustules were present on the patient's scalp, forehead, neck, arms and legs (figure 1). The patient had a prognathic profile

BACKGROUND

Idiopathic gingival fibromatosis is a rare hereditary condition with no definite known cause.¹ This condition may manifest as an autosomal dominant or, less commonly, an autosomal recessive mode of inheritance, presenting either as an isolated disorder or as part of a syndrome. Idiopathic gingival fibromatosis is a gradually progressive benign enlargement that affects the marginal, attached, as well as interdental papilla. The fibromatosis may potentially cover the exposed tooth surfaces, thereby hampering the functioning of the stomatognathic system. The gingiva appears pink and non-haemorrhagic, with firm and fibrotic consistency. We report a case of unusual non-syndromic presentation of generalised fibrotic gingival enlargement in a psoriatic patient, with a possible association between the two conditions.

CASE PRESENTATION

A 27-year-old woman presented with severely protruding teeth and gingiva since childhood, involving both her primary and permanent dentition primary and permanent dentition, along with difficulty in mouth closure and oral hygiene maintenance. The eruption and exfoliation sequence was normal. She also suffered from psoriasis for the past 12 years, with periods of remission interspersed with exacerbations. She would get

Figure 1 Psoriatic patches on extremities—psoriatic patches on hands, legs with disfigured fingers and toe joints, suggestive of positive arthropathy.

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with depressed nasal bridge and nose tip. Intraoral findings revealed bulbous, fibrotic enlargement of maxillary and mandibular gingiva. Her teeth were partially embedded within the enlarged gingiva, with occlusal of only one-third of the posterior teeth, and only the labial surface of the anterior teeth visible (figure 2). Indentations of the upper teeth were present in the lower gingiva due to constant trauma from occlusion. Other findings included a gummy smile, anterior open bite, spacing between the teeth and fissuring of the tongue.

INVESTIGATIONS

Orthopantomograph findings were not significant, however, they did show generalised mild interdental bone loss (<20%, approximately 1–2 mm loss of supporting bone) and increased spacing between the teeth. Routine haemogram was normal except for mildly increased platelet count and raised erythrocyte sedimentation rate (43 mm/h).

FINAL DIAGNOSIS AND TREATMENT

As we could not attribute this oral presentation to any known aetiology due to non-contributory family, medical, prenatal and drug history and investigations, we arrived at a provisional diagnosis of generalised severe fibrotic gingival enlargement of an idiopathic nature.

OUTCOME AND FOLLOW-UP

The case was discussed for further management with the periodontologist. Gingivectomy with aesthetic correction was advised but, in spite of repeated attempts at motivation, the patient was not willing to undergo surgical correction or to have a biopsy, hence we could not arrive at a conclusive diagnosis in this case. She could not attend follow-up visits owing to financial constraints. On telephonic follow-up 3 years after her presentation,

she reported significant reduction of her gingival enlargement and remission of the psoriatic lesions. However, she did not return for further management.

DISCUSSION

Psoriasis is a common chronic inflammatory skin disorder with periods of exacerbation and remission; it is estimated to affect 1–3% of the world's population.² It is a multifactorial disease appearing in the second and third decades of life, and, in one-third of patients, it reveals a strong genetic influence.^{2–3} The most common oral mucosal psoriasis lesions include fissured tongue, gingival and mucosal erosions, ulceration and, occasionally, inflammatory temporomandibular joint lesions.⁴ Oral lesions in psoriasis are rare, and presence of specific oral manifestations has been a subject of controversy.^{5–6} This may be because they are usually asymptomatic and do not come to the clinician's attention. The epithelial turnover time is significantly increased in psoriatic plaques and may be as rapid as 3–7 days, when compared to the normal epithelial turnover time of 28 days. This abnormally increased turnover time in psoriasis approximates that of the normal regenerative time of oral epithelium, and this possibility may also account for apparent lack of changes in the oral mucosa of patients with psoriasis.⁷ Even though some authors accept the existence of oral lesions as a manifestation of psoriasis based on histopathological similarities between them, others claim that oral lesions need to follow a parallel course to the cutaneous disease to be accepted as the same entity.⁸

Our patient developed psoriatic lesions on her skin at 15 years of age, and also presented with mild fissuring of the tongue, but this was preceded by generalised fibrotic enlargement of the gingiva since childhood. As her family, medical, postnatal and drug history ruled out the common causes of generalised gingival enlargement, we speculated on whether the gingival enlargement occurred as a predecessor to the psoriasis. As the patient in our case did not undergo biopsy or genetic mapping, strong evidence to suggest any conclusive diagnosis and its correlation or coexistence with psoriasis is sparse. To the best of our knowledge, this is the first case reported so far where psoriasis coexisted with idiopathic gingival fibromatosis. A thorough literature search was carried out to understand the disease process of psoriasis and its possible association with the development of gingival fibromatosis. To our surprise, we found some interesting similarities in the pathogenesis of both the conditions, which strengthened our speculations.

Pathogenesis of gingival fibromatosis

We can broadly classify gingival fibromatosis (GF) as drug-induced GF, leukaemic GF, hereditary GF and non-hereditary syndrome-associated GF, as shown in (table 1).^{9–12} Use of the term 'idiopathic fibromatosis' is recommended for GF that does not have a known cause. Clinical increase of gingival volume is due to the enlargement of epithelium and connective tissues. The cell interactions determine the accumulation of gingival tissue through two main pathogenic pathways: (1) excessive synthesis of extra cellular matrix (ECM) and (2) decrease of its breakdown. Recently, epithelial to mesenchymal transition (EMT) has been proposed as another pathogenic pathway promoting gingival fibrosis.¹³

EMT is a process in which epithelial cells transdifferentiate into fibroblast-like cells.¹⁴ EMT occurs in three distinct biological settings with different functional consequences: (1) type 1 EMT acts during implantation, embryogenesis and organ development, and can generate mesenchymal cells (primary

Figure 2 Fibrotic gingival enlargement—bulbous, fibrotic enlargement of both maxillary and mandibular gingiva more towards the palatal and lingual side. Spacing between the teeth seen. Mild fissuring on tongue seen.

Table 1 Gingival fibromatosis

Drug-induced GF

- A. *Anticonvulsants*—phenytoin sodium, carbamazepine, ethosuximide, sodium valproate, primidone, fenoprofen, felbamate, mephenytoin, mesuximide, phenobarbital, phenoximide
- B. *Immunosuppressants*—cyclosporin A
- C. *Calcium channel blockers*—nifedipine, amlodipine, bepridil, felodipine, nitrendipine, nifedipine, verapamil, nimodipine

Leukaemic GF

Leukaemic infiltration of gingiva may produce GE in these patients with a prevalence rate of 3.6%. Highest incidence of GE is seen in acute monocytic leukaemia (66.7%)¹²

Hereditary GF

- A. Lysosomal storage disorders
- ▶ I-cell disease (mucopolidosis II)
 - ▶ Mucopolysaccharidoses (Hurler syndrome/Scheie syndrome/Hunter syndrome/Maroteaux-Lamy syndrome/Sly syndrome)
 - ▶ Fucosidosis
 - ▶ Aspartyl glucosaminuria
 - ▶ Cowden syndrome
 - ▶ Menkes kinky hair disease
 - ▶ Ligneous periodontitis
 - ▶ Anderson-Fabry disease
 - ▶ α Mannosidosis
- B. Vascular/haematopoietic disorders
- ▶ Primary amyloidosis
 - ▶ Sturge-Weber angiomas
 - ▶ Klippel-Trenaunay syndrome
- C. Endocrine disorder
- ▶ Donohue syndrome (also known as Leprechaunism)
- D. Cutaneous disorder
- ▶ Tuberous sclerosis
 - ▶ Fraser-Francois syndrome Winchester syndrome
- E. Multisystem disorders
- ▶ Niemann-Pick disease
 - ▶ Gangliosidosis
 - ▶ Borroni dermato cardio skeletal syndrome

Non-hereditary syndrome-associated GF

Name of syndrome	Aetiology	Characteristic features in addition to GF
Isolated gingival fibromatosis with distinctive facies	Autosomal recessive	Brachycephalic, bushy eyebrows, hypertelorism, down standing eyes, flat bridge nose, high arched palate
Gingival fibromatosis with progressive deafness	Unknown	Deafness
Gingival fibromatosis—hypertrichosis syndrome	Autosomal dominant	Hypertrichosis usually on back and limbs
Murray-Puretic-Drescher syndrome (juvenile hyaline fibromatosis)	Autosomal recessive	Multiple hyaline fibromas, osteolysis of terminal phalanges, recurrent infection, stunted growth and premature death
Cross syndrome/Cross-McKusick-Breen syndrome	Autosomal recessive	Microphallia, mental retardation, athetosis and hypopigmentation
Rutherford syndrome	Autosomal recessive	Corneal dystrophy, delayed primary tooth eruption and failure of secondary teeth to erupt
Jones syndrome	Autosomal dominant	Progressive deafness
Zimmermann-Laband syndrome	Autosomal dominant	Deformed ears, hypoplastic nails, short fingers, hypertrichosis, delayed tooth eruption, high arched palate, mental retardation, mild hirsutism and hepatosplenomegaly
Ramon syndrome	Autosomal recessive	Cherubism, mental retardation, epilepsy, hypertrichosis, shunted growth, eye abnormalities
Pfeiffer's syndrome	Autosomal dominant	Premature coronal synostosis, turribrachycephaly (high prominent forehead) and maxillary hypoplasia
Epidermal nevus syndrome/Nevus sebaceous syndrome	Autosomal dominant	Hamartomatous Nevi, involvement of nervous skeletal and ophthalmic system
Ichthyosis follicularis, atrichia and photophobia (IFAP)	X-linked recessive	Ichthyosis follicularis, alopecia and photophobia
Costello syndrome	Autosomal dominant	Delayed development and intellectual disability, loose folds of skin, flexible joints and distinctive facial features including a large mouth
Cornelia de Lange syndrome	Autosomal dominant	Delayed development, severe intellectual disability, skeletal abnormalities involving the arms and hands, hypertrichosis and distinctive facial features
Schinz-Giedion syndrome	Unknown	Midface retraction, neurological problems, and organ and bone abnormalities
Neurofibromatosis	Autosomal dominant	Café-au-lait skin pigmentation, Lisch nodules in iris, growth of tumours along nerves in the skin, brain and other parts of the body

GF, gingival fibromatosis.

mesenchyme) followed by secondary epithelia after the mesenchyme undergoes a reverse mesenchymal epithelial transition; (2) type 2 EMT acts as a source of fibroblasts and other related cells involved in tissue regeneration and organ fibrosis in

response to persistent inflammation; (3) type 3 EMT occurs in neoplastic cells that have undergone genetic and epigenetic changes, notably of oncogenes and tumour suppressor genes and contributes to cancer progression and metastasis.¹³ A main

distinction between the first two types of EMT is that type 1 EMT produces mesenchymal cells, whereas type 2 EMT results in fibroblasts in mature tissues. In oral tissues, type 1 EMT is associated with palate and root development, type 2 EMT may play a contributory role in GF and oral submucous fibrosis and type 3 EMT is responsible for progression, invasion and poor prognosis of oral squamous cell carcinoma.¹³

The main trigger for type 2 EMT is the cytokine bath released in response to persistent inflammation. Inflammatory injury results in the recruitment of a diverse array of cells (mainly resident fibroblasts and macrophages) that release growth factors (tissue growth factor-TGF- β , platelet-derived growth factor-PDGF, epidermal growth factor-EGF, fibroblast growth factor-FGF-2) and metalloproteinases (MMP2, MMP3 and MMP 9).¹⁵ TGF- β 1 plays a key role in initiation of EMT. It is only found in the initial periods, leads to loss of cell-cell adhesion through inhibition of E-cadherin gene expression and decrease of adherent junctions, tight junctions and desmosomes. TGF- β 1 acts as a strong profibrogenetic factor through several mechanisms: (1) direct stimulation of collagen synthesis after the increase of a number of highly collagen synthesising fibroblasts through EMT; (2) in overexpression of MMP2 and MMP9, which are able to digest proteins (collagen IV and laminin) from basement membrane (BM) in the epithelium; loss of BM integrity is essential for the increased interactions between epithelial and connective tissue layers that contribute to fibrosis; and (3) in initiation of connective tissue growth factor-CTGF control on collagen synthesis.¹³ CTGF/CCN2 is a member of the CCN family, which contains conserved cysteine-rich domains and has various biological activities, important to stimulate proliferation of diverse cell types and to promote fibrosis.¹⁶

Delaminated epithelial cells then migrate towards the disruptions of the BM. This results in changes in gene expression that induce the loss of proteins associated with the epithelial phenotype and increased expression of proteins associated with a mesenchymal and migratory cell phenotype with concomitant alterations in cytoskeletal organisation, cell adhesion and production of ECM. In GF, TGF- β /Smad/Snail is a key signalling pathway for gingival-myofibroblast transdifferentiation.¹⁵ Subsequently E-cadherin, cytokeratin, claudin and occludin are repressed, while FSP1 (fibroblast-specific protein-1), vimentin, fibronectin and MMPs are increased.¹⁷ The accumulation of collagen and fibronectin in the ECM is caused by the lack of balance between MMPs and their inhibitors (TIMP), 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 has been proposed as a possible mechanism of fibrosis in GF.

The pathogenesis of psoriasis and its comparison with the disease process of GF

Psoriasis is characterised by keratinocyte hyperproliferation, dedifferentiation, neoangiogenesis and inflammation. T cell-mediated immunity, in which cytokines play an essential role, is considered to be the key element in the disease process.² Fibroblasts from psoriatic skin but not from normal skin can induce hyperproliferation of normal keratinocytes. Fibroblasts from uninvolved psoriatic skin proliferate faster than normal fibroblasts in the presence of normal human serum and proliferate to an even greater extent in the presence of serum from psoriatic patients.¹⁸ This evidence supported our assumption about the possible T-lymphocyte stimulation in our patient, which

induced fibroblasts to cause epidermal hyperproliferation, resulting in increased collagen production in gingiva leading to gingival hyperplasia.¹² Hyperproliferation of keratinocyte, also seen in gingival hyperplasia, has two important functions. First, it ensures a continuous regeneration of keratinocytes, the regenerative capacity of the epithelium. Second, epithelial proliferation can contribute to fibrosis by maintaining a cell pool to replace those cells involved in EMT and transform them into fibroblasts.

In psoriasis epidermis, there is reduced TGF β signalling, which potentiates keratinocyte hyperproliferation and results in increased TGF β 1 ligand in the epidermis and the serum.¹⁹ The increased TGF β 1 could also come from activated endothelial cells, fibroblasts or inflammatory cells in psoriasis patients. Similar findings were also seen in pathogenesis of GF, where increased TGF β 1 was the key factor for initiation of EMT, and in turn, fibromatosis of gingiva.

In addition to this, an interesting finding through a study by Joyce *et al*²⁰ showed two key micro-RNAs, miR-203 and miR-205, function in critical ways in psoriasis pathogenesis. miR-205 is expressed primarily in the basal layer of psoriatic uninvolved skin and has a role in maintaining the expansion of skin stem cells by antagonising negative regulators of PI(3)K signalling, an intracellular signalling pathway important in regulating the cell cycle. This miR-205 upregulation in psoriatic skin has been shown to target ZEB1 and ZEB2, which are both transcriptional repressors of E-cadherin, thus inducing epithelial-to-mesenchymal transition, which points to its potential role in psoriasis pathogenesis.²¹ The spatial patterns of miR-205 in psoriatic skin suggest a role in keratinocyte differentiation.²¹

Likewise, overexpression of certain cytokines such as tumour necrosis factor- α , Interleukins (IL-6, IL-8), PDGF, transforming growth factor- α , vascular endothelial growth factor, basic fibroblast growth factor and decreased expression of certain metalloproteinase (MMP1), are commonly seen in severe forms of psoriasis and GF.^{12 22–24} Moreover, human leucocyte antigen-polymorphism is seen in psoriasis and gingival hyperplasia.^{12 25}

Thus, overlapping of the pathogenic mechanisms involved in both these conditions raises a research question of whether a possible causal association of GF with psoriasis exists. Psoriasis is a distressing dermatological disorder that may cause a paranoiac effect on a patient's physical and mental well-being, and carries a social stigma. Unfortunately, our patient also suffered from generalised fibrotic gingival enlargement, which worsened the situation. Even though our case report could not provide objective evidence and there was lack of support from a review of the literature, this appears to be an interesting area for future research, for a possible link between the genetic and molecular basis of these conditions.

Learning points

- ▶ A possible association of T cell-mediated immunity in gingival enlargement and in the disease process of psoriasis.
- ▶ Gingival enlargement can be included among the oral lesions of psoriatic disease.
- ▶ Psoriasis and fibrotic gingival enlargement are both associated with the epithelial to mesenchymal transition.

Competing interests None declared.

Patient consent Obtained.

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