原文題目(出處)：	Oral Submucous Fibrosis: Review on Etiopathogenesis. J Canc Sci Ther;1:72-7.
原文作者姓名：	Dyavanagoudar SN
通訊作者學校：	Department of Oral Pathology, Sri Hassanamba Dental College and Hospital, Vidyanagar, Hassan, Karnataka, India
報告者姓名(組別)：	洪崇勛 (Intern G組)
報告日期：	99/4/13

內文：

Introduction

1.High risk precancerous condition
2.Changes in the connective tissue fibers of the lamina propia and deep parts leading to stiffness of the mucosa
3. Restrict mouth opening, seen dominantly in Asian people.
4. Predominantly seen in India, Bangladesh, Sri Lanka, Pakistan, Taiwan, China and among other Asiatics, with a reported prevalence ranging up to 0.4%
5. Major etiological factor: chewing areca nut (Areca catechu) (Caniff and Harvey, 1981).
6. In 1980 Indian market, the using of both areca quid products, Pan masala (Areca quid) and Gutkha (AQ tobacco) lead to increased incidence of OSF (Gupta et al., 1998).
7. Pan Masala (Areca quid):
includes areca nut, catechu, lime, flavors and spices
→ highest relative risk (489.1) of development of OSF (Hazare et al. 1998).
8. Gutkha (AQ + T):
contains all ingredients of Pan Masala (AQ) + tobacco+ other
is known as Kharra/ Mawa (Sinor et al., 1990)
9. The Indian market for Pan masala (AQ) and Guthka (AQ + T) is worth 25 billion (US$ 500 million) (Gupta and Ray, 2004).
→ the disease was classified as an idiopathic disorder (Schwartz, 1952).

Mortality/morbidity

1. High rate of morbidity
→ because of progressive inability to open the mouth
→ resulting in eating and consequent nutritional deficiencies.
2. Transform into oral cancer, particularly squamous cell carcinoma, at a rate of 7.6%.
3. symptom/sign:
• Progressive inability to open the mouth (trismus) due to oral fibrosis and scarring
• Oral pain and a burning sensation upon consumption of spicy foodstuffs
• Increased salivation
• Change of gustatory sensation
• Hearing loss due to stenosis of the eustachian tubes
• Dryness of the mouth
• Nasal tonality to the voice
• Dysphagia to solids (if the esophagus is involved)
• Impaired mouth movements (eg, eating, whistling, blowing, sucking)

Laboratory findings:
• Decreased hemoglobin levels
• Decreased iron levels
• Decreased protein levels
• Increased erythrocyte sedimentation rate
• Decreased vitamin B complex levels

Pathogenesis

1. Clinical features :fibrosis and hyalinization of subepthelial tissues
2. Changes in the extracellular matrix (ECM) hypothesis:
   The increased collagen synthesis or reduced collagen degradation
   → possible mechanisms in the development of the disease
3. Quid : substance or mixture of substances placed in the mouth or chewed and remaining in contact with the mucosa
   → usually containing one or both of the two basic ingredients tobacco and/or areca nut in raw or any manufactured or processed form (Zain et al., 1999).
4. Areca nut alkaloids: arecoline, arecadine, arecolidine, guyacoline and guacine (IARC anonymous, 1985).
5. Flavonoid(黃酮類) components in areca: tannins and catechins
6. These alkaloids undergo nitrosation and give rise to N-nitrosamine which might have cytotoxic effect on cells (Hoffmann et al., 1994)
7. Betal quid chewing 15~60 min x 5~6 time/day
   → alkaloids from the quid are absorbed into the mucosa
   → microtrauma produced by the friction of coarse fibers of areca nut facilitates diffusion of the alkaloids into the subepithelial connective tissue
   → juxtaepitheial inflammatory cell infiltration (Chiang et al., 2002).
8. healing process fails to occur
   → fibrosis may be considered as a irreversible state of tissue alteration
   → these actions of ECM derive from its ability to sequester and modulate the activity of specific growth factors (Nathan and Sporn, 1991).
9. Transforming growth factor-β (TGF-β):
   synthesis and degradation of ECM
   in response of cells to ECM mediated through integrin receptors

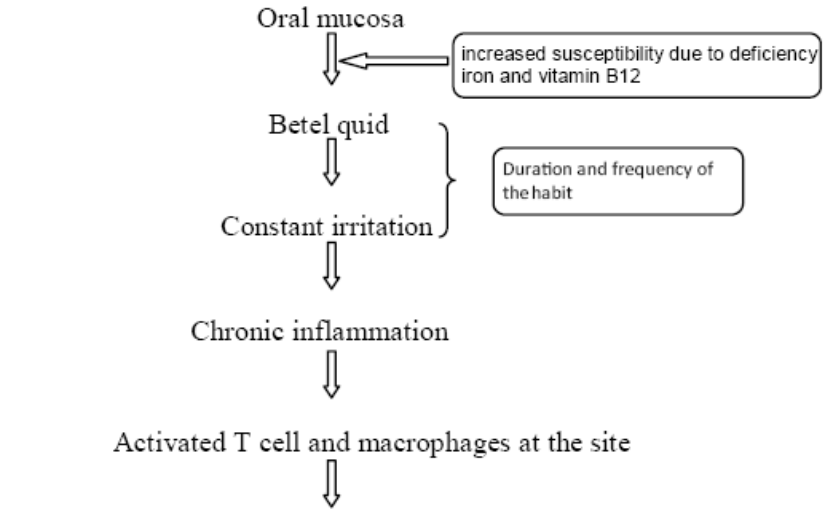

Figure 1: Initial events of the disease process oral mucosa which is in direct contact with the betel quid due to the habit, is the site of constant irritation (Rajalalitha and Vali, 2005).

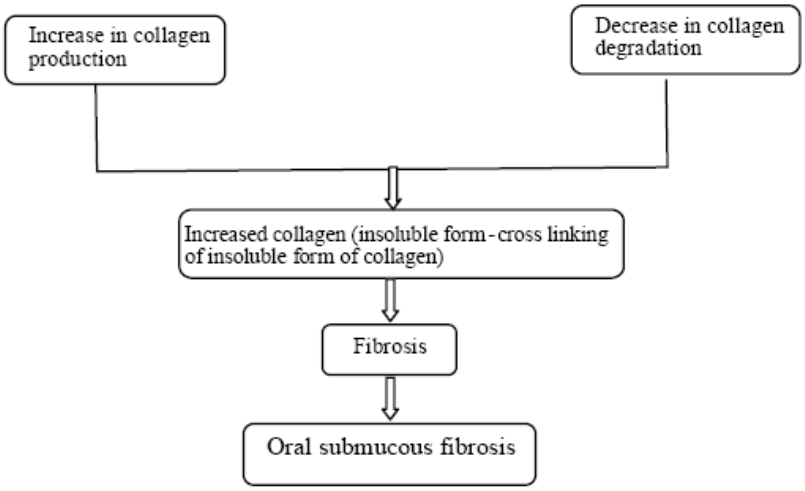

Figure 2: Overall effect of activated TGF beta pathway. There is in increase n collagen production and cross linking (insoluble form) along with the decrease in the collagen degradation. This produces increased collagen deposition in the subepithelial connective tissue layer of the oral mucosa leading to OSF

Collagen production pathway

1. 3 main events in this pathway :
   activation of procollagen,
   elevation of procollagen proteinase levels
   up regulation of lysyl oxidase (LOX activity).
2. Collagen:
   * most abundant protein in the human body
   * structural element of connective tissue
   * triple helix stabilized by unusual crosslink
3. Procollagen genes are transcribed and translated to form procollagen monomeric chains

4. The genes COL1A2, COL3A1, COL6A1, COL6A3, COL7A1 have been identified as definitive TGF-β targets (Rajalalitha and Vali, 2005).
5. TGF-β activate procollagen genes
   → expression of procollagen genes and hence collagen level↑ in OSF
6. Procollagen proteinases ↑
   → such as PCP cleaves C-terminal and PNP's (PNP1 and PNP 2) cleaves N terminal play essential role in pathogenesis of OSF
   → TGF-b may play an important role in inducing fibrotic tissue formation,
7. Yi-Ting et al., (2009) found arecoline stimulated connective tissue growth factor (CTGF) production in buccal mucosal fibroblasts (BMF).
8. BMFs →producing CTGF during arecanut chewing. →pathogenesis of OSF
9. Arecanut chewing →TGF-β↑due to inflammation →CTGF synthesis
10. Curcumin (major yellow pigment in turmeric, curry and mustard)：
    1. High antioxidant and anti inflammatory activity
    2. Widely used as a flavoring and coloring agent in foods and as an herbal medicine to treat chronic inflammatory diseases (Goel et al., 2008)
    3. Inhibiting CTGF gene expression →activated hepatic stellate cells →suppress the expression of extracellular matrix genes
11. Curcumin could completely inhibit arecoline-induced CTGF synthesis and the inhibition is dosedependent (Chen and Zheng, 2008).

Up-regulation of LOX

1. Areca nut chewers had significantly raised levels of copper when compared with the control subjects (Trivedy et al., 2000).
2. Excess copper is found in tissues of other fibrotic disorders– Wilson's disease, Indian childhood cirrhosis and primary biliary cirrhosis.
   → copper dependent enzyme plays a key role in collagen synthesis and its cross linkage
3. Copper added at various concentrations in vitro has also been shown to increase proliferation of fibroblasts in culture
   (Trivedy et al., 2001).
4. Fibroblasts doubling time : OSF < normal
5. The process of cross linking
   ＊gives tensile strength and mechanical properties to the fibers
   ＊makes the collagen fibers resistant to proteolysis

Collagen degradation pathway

1. Activation of inhibitor of matrix metalloproteinase gene TIMPs
2. Activation of plasminogen activator inhibitor PAI gene.

Upregulation of cyclo-oxygenase(COX-2)

1. Biopsies from buccal mucosa of OSF stained for COX-2 by immune histochemistry
   →increased expression of the enzyme in moderate fibrosis and disappeared in advanced fibrosis
2. Alkaloid (areca-nut) exposure of buccal mucosal fibroblasts may result in the accumulation of collagen (Harvey et al., 1986).
3. Collagenase activity has been found to be reduced in OSF than in normal oral mucosa (Shieh and Yang, 1992).
4. OSF may be considered a collagen-metabolic disorder resulting from alkaloid exposure and individual variation in collagen metabolism.

Role of Heat shock proteins (HSP) in pathogenesis of OSF

1. HSP47, is a 47 kDa collagen-binding heat shock protein
2. HSP47 is a molecular chaperone that is specifically involved in the processing and quality control of collagen molecules
   (Shung et al., 2008)
3. Arecoline is capable of stimulating HSP47 mRNA expression in human BMFs
4. Arecoline could enhance collagen synthesis in human gingival fibroblasts (Chang et al., 1999).
5. HSP47 mRNA was upregulated by arecoline in human BMFs
   areca quid chewing →simultaneous effect on HSP47
   →accumulation of collagen in oral mucosal connective tissue

Role of basic fibrobalstic growth factor (bFGF) in pathogenesis of OSF

1. FGFs interacts synergistically with other growth factors, having an effect on extracellular matrix (ECM) deposition
2. bFGF modulate the endothelial cell integrin or VEGF-receptor
   → directly stimulate endothelial cell proliferation or facilitate VEGF–endothelial cell interaction (Salcedo et al., 1999).
3. endothelial cell derived IL-1 and bFGF modulate fibroblast properties independently
   → altered endothelial cell–fibroblast communication may be involved in the pathogenesis of fibrosis
   (Wojas-Pelc and Lipko-Godlewska, 2005).
4. Mast cells found in the early stages of OSF :
   Primary source of heparin
   May serve as a significant source for heparin binding growth factor, the bFGF, in disease processes (Qu et al., 1995).
5. While bFGF was autorepressive and catabolic
   → TGFb was autoinductive and anabolic
   representing part of feedback mechanism (Silverio-Ruiz et al., 2007).
6. Contrary to this effect, bFGF was most potent growth factor in increasing proliferation, lycosaminoglycans synthesis and promoting collagen synthesis in TMJ disk cells (Detamore and Athanasiou, 2004)

Precancerous nature and malignant transformation

1. First described by Paymaster in 1956 when he observed slow growing squamous cell carcinoma (SCC) in 1/3 of the patients with the disease
2. 5 criteria to prove the disease is precancerous：
   high occurrence of OSF in oral cancer patients
   higher incidence of SCC in patients with OSF
   histological diagnosis of cancer without any clinical suspicion in OSF high frequency of epithelial dysplasia
   higher prevalence of leukoplakia among OSF cases
   (Pindborg et al., 1967).
3. Malignant transformation rate of OSF: range of 7–13%,
   long term：7.6% over a period of 17 years (Murti et al., 1985)
4. It could be assumed that carcinogens from areca diffuse into deeper tissues in a longer duration.
   → Less vascularity may deny the quick absorption of carcinogens into the systemic circulation (Tilakaratne et al., 2006).
5. Pre-cancerous epithelial cells acquire multiple genetic mutations
   Associated stroma becomes “activated” commonly expressing myofibroblastic

markers (Ronnov-Jessen et al., 1996)

6. Activated carcinoma-associated fibroblast are presumed to express:
   smooth muscle actin
   ECM proteins
   growth factors
   that act in an autocrine and paracrine fashion to potentiate and support the survival of a tumor (Bhowmick et al., 2004)

Treatment

1. When mouth opening is severely limited
→ surgical interventions, such as myotomy, coronoidectomy and excision of fibrotic bands, are required.
2. Alternative procedures, such as
insertion of an oral stent,
physiotherapy
local heat therapy
mouth exercises using acrylic carrots and ice cream sticks
have been tried with variable rates of success

Treatment	Treatment Details
Micronutrients and minerals	Vitamin A, B complex, C, D and E, iron, copper, calcium, zinc, magnesium, selenium and others
Lycopene	6 8 mg twice a day for 2 months
Pentoxyfilline	400 mg 3 times a day for 7 months
Interferon gamma	Intralesional injection of interferon gamma (0.01–10.0 U/mL) 3 times a day for 6 months
Steroids	Submucosal injections twice a week in multiple sites for 3 months
Steroids	Topical for 3 months
Hyalase + dexamethasone	-
Placental extracts	Turmeric30 Alcoholic extracts of turmeric (3 g), turmeric oil (600 mg), turmeric oleoresin (600 mg) daily for 3 months
Chymotripsin, hyaluronidase and dexamethasone31	Chymotripsin (5000 IU), hyaluronidase (1500 IU) and dexamethasone (4 mg), twice weekly submucosal injections for 10 weeks

Table 2: Treatment modality for OSF (Auluck et al., 2008).

3. Therapy consisting of a combination of the above-mentioned drugs and surgery might be useful.

Conclusion

1. Main etiological factors for OSF are the constituents of areca nut, mainly arecoline, whilst tannin may have a synergistic role
2. These chemicals interfere with the molecular processes of deposition and/or degradation of extracellular matrix molecules such as collagen, causing imbalance in the normal process
   → reduced phagocytosis of collagen by fibroblasts
   up or down regulation of key enzymes
3. Process may also be influenced by :
   increased secretion of inflammatory cytokines, growth factors
   decreased of anti-fibrotic cytokines
4. Nutritional deficiencies could synergies the symptomotology by contributing to epithelial atrophy.
5. The individual mechanisms operating at various stages of the disease–initial, intermediate and advanced–need further study in order to propose appropriate therapeutic interventions.

題號	題目
1	Where isn't the prevalent area of OSF? (A) Indian subcontinent (B) Southeast Asia (C) North America (D) Taiwan
答案(C)	出處：oral and maxillofacial pathology 2nd edition
題號	題目
2	Which choice is improper for OSF ? (A) Trismus (B) No relationship with malnutrition (C) Chronic inflammation (D) Is prone to develop oral CA
答案(B)	出處：oral and maxillofacial pathology 2nd edition