ORIGINAL RESEARCH PAPER
Volume - 10 | Issue - 01 | January - 2021 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

ORAL MUCOSAL FIBROSIS : A REVIEW

Dental Science

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ABSTRACT

Fibrosis is the end result of various chronic inflammatory reactions. It hardens and / or scars tissue and is attributed to excessive deposition of extracellular matrix components, mainly collagen. Stimuli of fibrosis include persistent infections, autoimmune reactions, allergic reactions, chemical attacks, radiation, and tissue damage. Most common fibrotic lesion of oral cavity is oral submucosal fibrosis. Others include scleroderma, radiation induced fibrosis etc. Though fibrosis of mucosa may be identified by clinical features such as thinning and stiffening of mucosa, accurate degree of fibrosis may need the use of imaging modalities such as Ultrasonography using which we can determine the alteration in the thickness and the echogenicity of the dermis and it can be considered as a valuable tool to determine the extent and severity in of fibrosis. This is a review article on various fibrotic lesions involving oral mucosa.

KEYWORDS

Fibrosis, Submucosa, Ultrasonography

INTRODUCTION

Fibrosis is defined as the overgrowth, stiffness, and / or scarring of various tissues and is attributed to the over-deposition of the extracellular matrix components including collagen. [1] Most chronic fibrotic disorders present with persistent irritation caused by various etiologies that support the assembly of growth factors, proteolytic enzymes, angiogenic factors, and fibrogenic cytokines. Following which the deposition of connective tissue elements that progressively remodel and destroy normal tissue architecture takes place.[1] Etiological factors can vary, including infections, autoimmune reactions, toxins, radiation, and mechanical injuries.[1] In oral cavity most common cause of fibrosis are oral submucous fibrosis, radiation induced fibrosis, scleroderma, wound healing etc. The event of fibrosis is characterized by cellular and extracellular architectural changes which will be objectively measured via impractical biopsies or via new advanced imaging. Since these are usually diffuse lesions, it is neither possible nor ethical to perform a biopsy from all sites in all patients to allow for histopathological evaluation for the diagnosis of these lesions. Also, the biopsy may not be 100% representative of disease severity in a widespread disease. Also there are chances that there is scarring and increased fibrosis at the actual site of biopsy. For these reasons, there is growing interest in developing non-invasive diagnostic methods for fibrotic lesions.[2] Since ultrasound examination (USG) is non-invasive and safe, it has better patient acceptance. Ultrasonography is particularly suitable for imaging superficial structures of the head and neck region. USG offers both qualitative and quantitative ratings.

Classification of fibrosis of skin & mucous membrane[3]

- Scleroderma
  - Systemic scleroderma
    - Progressive systemic sclerosis
    - CREST syndrome
  - Localized scleroderma (morphea)
    - Plaquelike morphea
    - Linear morphea
    - Generalized morphea
- Sclerodermalike skin changes
  - Other connective tissue diseases
    - Mixed connective tissue disease
    - Overlap syndromes with lupus erythematosus and dermatomyositis
    - Eosinophilic fasciitis
    - Idiopathic acro-osteolysis
- Metabolic and immunologic disorders
  - Chronic graft-vs-host disease
  - Porphyria cutanea tarda
  - Phenylketonuria
  - Carcinoid syndrome
  - Paraproteinemia
  - Juvenile-onset diabetes mellitus
- Chemically induced disorders
  - Bleomycin-induced skin fibrosis
  - Polyvinylchloride acro-osteolysis
  - Silicate skin fibrosis
- Connective-tissue hamartomas of the collagen type
  - Inherited
    - Familial cutaneous collagenoma
    - Shagreen patches in tuberous sclerosis
  - Acquired
    - Isolated collagenomas
    - Eruptive collagenomas
- Keloids and hypertrophic scars

Scleroderma

Progressive systemic sclerosis (PSS), conventionally called as scleroderma is a collagen disorder which is characterized by fibrosis of skin, mucosa, muscles, and internal organs such as the gastrointestinal tract, lungs, blood vessels etc.[4] This disorder is rare and involves oral and paraoral structures that form the distinct group of clinical manifestation. Oral changes include inability to open the mouth wide, reduced interincisal opening, tongue rigidity due to submucosal fibrosis and xerostomia due to fibrosis of salivary glands.[4] Antinuclear antibodies (ANA) are the most frequently detected autoantibodies in Scleroderma patients. Histopathological evaluation is not recommended in current practice because the clinical features are generally sufficient to make a correct diagnosis. In unclear and difficult to diagnose cases, a skin biopsy may be performed. Radiographic changes mainly include As usually there wille osteolysis of the mandibular arch and the coronary process. A panoramic radiograph should be performed in every case of scleroderma. Gastroparesis is a functional disorder of SSc cases and is confirmed in barium X-rays, scintigraphy or antroduodenal manometry.[5]

Radiation induced oral mucosal fibrosis

Oral mucosal fibrosis may appear as a late effect of radiation therapy. Radiation fibrosis syndrome (RFS) is a progressive fibrotic tissue sclerosis with various clinical symptoms in the irradiation field. It is usually a late complication of radiation therapy and can occur weeks or even years after treatment.[6] This can affect mouth opening and tongue and lip movement. Submucosa of Irradiated areas show increase in presence of fibrinous exudates, necrosis and vessel wall thickening. They have dense fibrosis, with predominantly thick fibers.[7]

Oral mucosal fibrosis associated with Crohn's disease

Crohn's disease is described as a disorder affecting "the mouth to the anus; although oral CD or CD isolated from the upper gastrointestinal tract remains relatively rare findings. One of the oral manifestations of Crohn's disease includes mucosal fibrosis.[8] fibrosis in Crohn's disease (CD) is due to ECM deposition and has been seen as a relatively slow process needing many months to develop, fibrosis follows the distribution and location of inflammation in gastrointestinal tract. The diagnoses of Crohn's disease is made on clinical grounds supplemented with objective findings of radiological, endoscopic, and histological examination.

Oral submucous fibrosis as an overhealing wound

Normal wound healing involves collagen deposition. However, it is excessive in fibrosis. Overhealing wound may be because of chronic

physical, chemical, and mechanical injury to the oral mucosa. Hemostasis or thrombosis is an essential step in healing and is performed by platelet aggregation and fibrin clot formation.[9] As a result of hemostasis, in mucosal and cutaneous injury, a fibrin rich granulation tissue forms and matures 64 in composition as the inflammatory phase takes place. At the end of inflammation, the wounds transfers to the proliferative phase. This is associated with the migration of keratinocytes and fibroblasts onto and into the wound bed respectively and fibroblasts secrete extracellular matrix.

Oral submucous fibrosis(OSMF)

Oral submucous fibrosis(OSMF) is one of the most common potentially malignant condition in India. It is a debilitating, progressive, irreversible collagen metabolic disorder induced by chronic chewing of areca nut and its commercial preparations; affecting the oral mucosa and occasionally the pharynx and oesophagus; leading to mucosal stiffness and functional morbidity; and has a potential risk of malignant transformation.[10] The hallmark of diagnosing OSMF is clinical and histological. As there are chances that scarring and increased fibrosis at the actual site of biopsy, histological investigation is rarely advised.

Ultrasonography and fibrosis

The main parameters that describe the interactions between ultrasound and the tissue through which it is transmitted are attenuation, velocity, and impedance. The attenuation and velocity are directly proportional to the the quantity of collagen present within the tissue and inversely proportional to the water content and this property is usually expressed as echogenicity which is the ability to bounce an echo.[11] Ultrasound echogenicities were described in comparison with adjacent structure as follows hyperechoic (brighter), Hypoechoic (dark), isoechoic (equal) and anechoic (no internal echoes) or mixed signals.[11] Collagen has greater modulus of elasticity as compared to other tissue which results in higher velocity and impedance and ultimately leads to more echogenicity.[12]

2D ultrasound outlines normal mucosa with a uniform fine mottled appearance with interspersed hypoechoic areas due to normal blood vessels and hyperechoic areas due to fibers, nerves, etc. Li et al., Used ultrasound to monitor localized scleroderma. The USG detected several abnormalities in the active lesions, including decreased blood flow, increased echogenicity and loss of subcutaneous fat, and reduction in lesion size during treatment. Hesselstrand R et al., used high frequency ultrasonography for assessment of systemic sclerosis (SSc).[2]

Ultrasonographic examination of scleroderma

In the case of scleroderma, clinical palpation may not detect the thickness of the skin / mucosa but rather changes in consistency, which could be due to increased interstitial water or matrix components. This could explain the lack of a relationship between the clinical score and the ultrasound reading in most of the locations examined. [13] The reliability of the ultrasound technique allows recognition of small and serial changes in the extent and nature of involvement.[13]

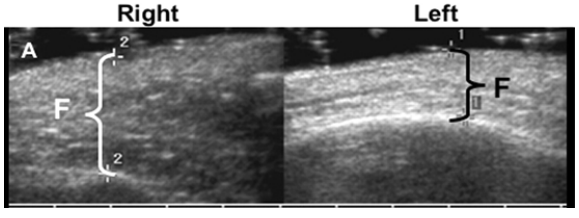

Fig 1: USG in the infra-orbital and malar region showing loss of subcutaneous fat on the affected left side compared with the unaffected right side in scleroderma[14]

Ultrasonographic examination of Radiation fibrosis syndrome

The main limitation of the current clinical assessment of fibrosis is the inherent subjectivity in observation and palpation. Ultrasound Nakagami imaging, which complements conventional B-mode imaging, has the potential of providing key imaging signatures for the characterization and quantification of radiation-induced neck fibrosis.[14] Nakagami-parameter imaging, which is a statistical tool that has been applied in the context of ultrasonic characterization of the biomechanical properties of backscattered radio-frequency (RF) signals from biological tissues.[15]

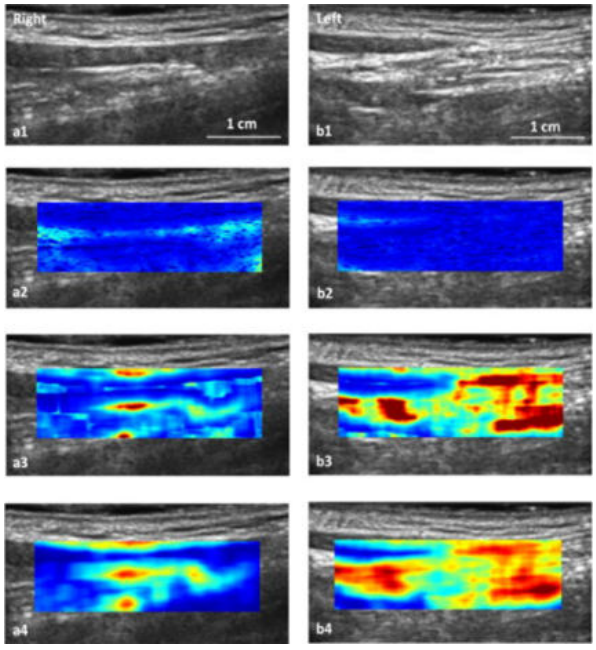

Fig 2: Nakagami imaging comparison of the right neck (right column) and left neck (left column) and. Row 1: B-mode image; Row 2: Nakagami-PDF image; Row 3: Nakagami shape image; and Row 4: Nakagami-scaling image. Compared with the right neck, lower Nakagami PDF and higher Nakagami shape and scaling parameter values were observed in the left neck area with fibrosis

Ultrasonographic examination of OSMF

Ultrasonographic examination of OSMF reveals definite increase in the echogenicity of the submucosal layer fibrous bands as hyperechoic band.

Fig 3. Ultrasonography demonstratig number (arrows), length (dot line) and thickness (dot line) of the fibrotic bands

Fig 3. Ultrasonography demonstrates diffuse fibrotic patch (crossing dot lines)

In a study conducted by C Kritika et al. in one patient who had areca chewing habit without clinical presentation of OSMF the submucosa appeared hyperechoic which suggests that USG can be used in early detection of OSMF which cannot be diagnosed clinically.[16]

Vascularity also plays significant role in the treatment prognosis of OSMF. Doppler will show poor respose in affected area with poor vascularity. More than average vascularity may suggest malignant changes. In the same study by Manjunath K et al. Ultrasonographic unit with color Doppler facilities and 9-5 MHz intra - cavitary convex transducer was used to depict the vascularity of submucosa in OSMF patients. Color Doppler shows the speed and direction of the erythrocytes at which they approach and move away from the transducer, and thus provides information necessary for the functional duplex sonography which is coded with blue and red color respectively.[2]

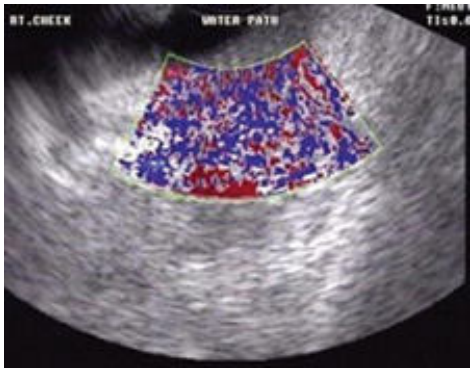

Fig 4. Ultrasonographic evaluation of normal buccal mucosa

There was reduced flow velocity and vascularity of mucosa overlying the bands was found to be decreased. Vascularity of mucosa in between bands was found to be normal.[11]

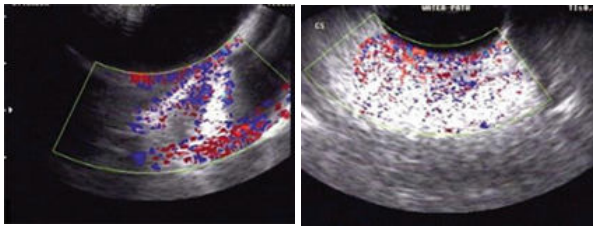

Fig 5. Diminished vascularity in an oral submucous fibrosis lesion

CONCLUSION

Conditions such as mucosal fibrosis where lesions are diffuse and disease severity varies from site to site in the same patient, requires a non-invasive and viable approach for effective evaluation. In addition to clinical and histopathological evaluation, ultrasound provides an entirely new third dimension, allowing for tissue characterization on the mucosa and indicating the depth of fibrosis in the tissue, which is not possible with other methods.

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