

Leading article

Oral submucosal fibrosis – a preventable disease

Oral submucosal fibrosis is a chronic, progressive, and irreversible disease of unknown aetiology. It affects oral, oropharyngeal, and at times oesophageal mucosa. The earliest description of the disease was by Schwartz in 1952,¹ and the first Indian cases were reported from Bombay² and Hyderabad.³ At the time the condition was thought to be caused by disordered growth of collagen. It has drawn greater clinical attention over the past 15 years and the purpose of this review is to reconsider its epidemiology, aetiology, and successful prevention.

Epidemiology

The disease occurs mainly in Indians. It affects between 0.2% and 1.2% of an urban population attending dental clinics in India,^{4,6} and epidemiological studies suggest an overall prevalence of up to 0.4% in such places as Kerala.⁴ In a more recent study⁷ of 50 000 villagers, which included patients with subclinical disease, the combined prevalence for men and women was 13/10⁵ person years. The total number of cases one is likely to see in India is around two million.⁸ Outside the subcontinent, cases have been reported among Indians living in Kenya, Malaysia, Uganda, South Africa, the Fiji Islands,⁴ and the UK.⁹⁻¹³ Ethnic clusters among Burmese and Pakistanis have been reported.¹⁴ Sporadic cases have been reported in other ethnic groups from countries such as Taiwan,¹⁵ Formosa, Nepal, Thailand, South Vietnam, and Sri Lanka.¹⁷ Consequently, the disease should be a cause for concern in countries with large migrant populations from South East Asia.

In Johannesburg and Pretoria, Shear *et al*¹⁸ have reported a prevalence of 0.5% in women. In Durban, where Indians constituted 46% of the population, Seedat *et al*¹⁹ found a prevalence of 3.4% when a large sample of the population was examined and subclinical cases were included. Most patients were in the age range of 45-54 years. In a study from London,¹³ which included 43 Indians (Indians 26, African Indians 17) and one Pakistani, 85% had classic clinical features of oral submucosal fibrosis. There are similar case reports of Indian immigrants in other parts of the UK⁹⁻¹³ – for example, three cases were diagnosed in Leicester in 1986,⁹ and one of whom presented with carcinoma. The patients were reluctant to be examined or investigated and this may explain the apparent lack of cases seen in gastrointestinal clinics and dental hospitals in Europe or North America. Betel nut and 'pan' are freely available in the United Kingdom, and in a city such as Leicester one might expect to find 3000 cases of oral submucosal fibrosis. The disease is rare in North America, and again most cases are in migrants from South East Asia or India.¹⁴ The disease has also been diagnosed among Europeans living in Hyderabad, India³ and in a British woman married to a Pakistani.²⁰

Aetiopathogenesis

The exact aetiology is unknown and subject to much speculation. Several hypotheses have been put forward. Caniff *et al*¹³ and Pindborg²¹ considered the disease to be a form of hypersensitivity to capsaicin, an irritant in chillies, but this was not totally substantiated in experimental work

on rats.²² Also, few cases have been reported from South Africa, Mexico, and Bihar, India where traditional diets contain substantial amounts of chillies. Nutritional and vitamin deficiencies have been mentioned as possible aetiological factors.^{23,24} Mucosal changes similar to those in vitamin B and iron deficiency are seen in oral submucosal fibrosis and seem analogous to sideropenic dysphagia.^{23,25} Tobacco chewing and smoking are not seriously considered to play a role as these habits are also common in the healthy population.¹⁶ Lal *et al*¹⁶ postulated, however, that use of 'pan' (betel leaf) and 'supari' (betel nut), may be important. Pan is betel leaf on to which slaked lime is smeared and this is wrapped over a mixture of betel nut and other additives such as tobacco powder, cardoman seeds, aniseed, or gambier (acacia catechu extract). It is chewed slowly and is often kept in contact with the oral mucosa for several hours. This social custom is followed by almost all classes of people and religions throughout the Indian subcontinent and the Far East. Betel is frequently used as a psychotropic and anti-helminthic agent¹³ and as an after meal digestant which is taken to ease abdominal discomfort. Shear *et al*¹⁸ and Caniff *et al*¹³ have also confirmed a positive association between betel nut chewing and the onset of oral submucosal fibrosis.

The alkaloid and tannin content of areca nuts (betel nuts) are responsible for fibrosis. The composition of nuts differs with the method of cultivation and preparation. Soaking and boiling, for instance, reduce the concentrations of tannins and alkaloids. It is likely that differences in concentrations of these chemical constituents may be responsible for regional variations in disease frequency.¹³ Also, sliced and chewed betel nut is more harmful than betel nut wrapped in the leaf. In the former, the alkaloids are in direct contact with the buccal mucosa for a longer time resulting in greater mucosal penetration.²⁷

Though the disease is multifactorial, it is probable that genetic and environmental factors influence its development.²⁵ In genetically predisposed people, betel nut and pan chewing render the oral mucosa susceptible to chronic inflammatory changes. The sequence of events is initiated by the alkaloid, arecoline, which stimulates fibroblast proliferation and collagen synthesis.²⁸ The flavanoid catechin²⁹ and tannins from betel nut then stabilise the collagen fibres and make them resistant to degradation by collagenase. The other alkaloid, arecardine, is considered to be the principal carcinogenic agent.³⁰ The occurrence of oral submucosal fibrosis even in the absence of intraoral influences such as betel chewing, smoking, or a high intake of spicy foods suggests that these are other factors including genetic influence and an increased frequency of HLA10, DR3, and DR7¹³ has been reported. The frequency of the disease may also be subject to hormonal influences as it has a greater frequency in women in ratio of 3:1.⁴

Immunological studies have shown raised IgA, E, and D values³¹ while IgG and M are usually normal. Autoantibodies to gastric and parietal cells, as well as thyroid microsomal, antinuclear, reticulin, and antismooth muscle antibodies have been found in 65% of patients with the disease.¹³

Rao³ and others¹⁵ considered the condition to be a localised form of collagen disease of idiopathic origin as in Peyronie's

disease, Dupuytren's contracture, retroperitoneal fibrosis, or idiopathic mediastinal fibrosis.

In view of the numerous factors suggested as possible causes, oral submucosal fibrosis is best regarded as a clinical syndrome rather than a distinct disease entity.

Pathology

Schwartz¹ described a fibrosing condition in the mouth of five East African women and gave it the Latin tag *atrophia idiopathica tropica mucosa oris*. It is synonymous with idiopathic scleroderma of the mouth²³ and juxtaepithelial fibrosis.³² In its early stages the palate looks white due to fibrous tissue.^{2,3,13,32} Patients may be asymptomatic and detected only by chance during routine dental checkup. As the disease progresses,^{3,13} fibrous tissue forms arches extending from the anterior pillars and tonsillar fauces into the soft palate. They appear as a delicate reticulum of interlacing strands which later become confluent. Fibrosis can also extend into the lateral wall of the pharynx via the pillars and down to the pyriform fossa. In time the soft palate and buccal mucosa lose their elasticity and resilience. When palpated from outside, the cheek feels tough and thickened, the soft palate shows restricted mobility and has a hard rubbery feel. The uvula is small and distorted. In advanced disease, thick inelastic fibrous bands develop vertically in the cheek. The floor of the mouth becomes pale and thickened and the tongue is reduced in size. Bands encircle the lips and distort their shape. At any stage of the disease the overlying mucosa may become the site of superficial ulceration, dysplastic change, and malignant transformation. Dysphagia occurs once fibrosis extends into the oesophagus and disordered motility is obvious at barium swallow.

Histopathological assessment¹³ of the buccal mucosa is made on biopsy specimens from the mandibular margin of the lower second molar tooth to avoid erroneous interpretation due to frictional keratosis. Changes include an atrophic epithelium in 86% of patients, defective keratinisation and dysplasia in 33%, and flattening of the dermal/epidermal junction in 27%. The atrophic process progresses into the deeper planes of the mucosa, extending from the lamina propria up to the underlying musculature, although the latter is frequently unaffected. Normal and abnormal collagen with varying degrees of colloid or amyloid degeneration and fragmentation may accumulate beneath the basement membrane. In due course these changes result in a decrease in the ground substance, cellular elements, and vascularity with progression to end stage fibrosis. Chronic inflammatory cells accumulate in the dermis in 60% of patients. Cell mediated immunity studies indicate that oral submucosal fibrosis is an intermediate stage in the transformation of normal cells to oral malignancy.³¹

Clinical features

Of particular concern is the fact that oral submucosal fibrosis affects young people. The mean age at presentation was 43 years.¹⁹ The reason is unclear. The percentage of chewers increases with age. It may be that the frequency of chewing and type of betel nut may have an influence on the individual's susceptibility. The earliest clinical feature^{3,11,12,21,25} is a burning sensation and discomfort in the oral cavity while eating highly seasoned foods. Gradually various parts of the mouth lose their natural suppleness and related disabilities develop. With involvement of the tongue, speech and associated functions are affected. Extension of fibrosis to other areas in the oral cavity results in difficulty in mastication, reduced salivation, dysphagia, pain in the ears, and loss of auditory acuity due to stenosis of the pharyngeal end of the eustachian tubes. In advanced cases with progressive in-

ability to open the mouth, whistling, blowing, and sucking movements are affected. The jaws may become inseparable and totally inelastic and patients can only maintain their nutrition by pushing food into the mouth. The buccal mucosa is frequently ulcerated and secondarily infected consequent to ischaemia and constant pressure of the mucosa against the buccal aspect of the teeth.

Oral submucosal fibrosis and carcinoma

There is a positive relation between the incidence of leukoplakia and carcinoma and the occurrence of oral submucosal fibrosis.³³⁻³⁵ In Bihar (Singhbum), where the incidence of the disease is low, leukoplakia occurred in only 0.2% of patients. The highest incidence of oral carcinoma is reported from Andhra Pradesh and Kerala where leukoplakia is also seen in greatest frequency.⁴ Altogether 12.7% of patients in Kerala⁴ had leukoplakia and 40% of 100 patients with oral cancer had oral submucosal fibrosis.²⁴ In Bombay, the reported figure was 26.6%.⁵ Betel leaf (pan) chewing accounts for 31% of oral cancers in Madras, South India. Its relation to oral submucosal fibrosis as a premalignant factor has not been specifically investigated but in a large survey in India in 1956³⁶ one third of oral cancer was causally related to this. McGurk and Craig report two female Asian immigrants to the UK who had oral submucosal fibrosis and subsequently developed oral cancer.¹²

Management

When the disorder is clinically suspected, histopathological confirmation is needed and subsequent long term surveillance should be at short intervals to detect dysplasia or early malignant change. Medical treatment is unhelpful¹³ and does little to prevent the onset of squamous cell carcinoma in the atrophic oral mucosa. Local hydrocortisone injection,¹⁵ hyaluronidase,¹⁵ placental extract,¹³ and vitamin and iron supplements¹³ have been used but with limited benefit.

Surgery^{13,37} is indicated when opening of the mouth is severely limited. Bilateral temporalis myotomy and coronoideotomy followed by split thickness skin grafting have been tried with some benefit.

The close association between betel leaf and nut chewing, oral submucosal fibrosis, and oral cancer indicate the need for a preventive approach through health education and increased awareness among the public of the serious consequences of these habits. The high prevalence of the disorder in the Indian subcontinent and South Africa would suggest a similar high prevalence in the UK and other countries with large migrant populations. In the UK, where the estimated Indian and Pakistani migrant population is about 670 000, one would expect to see many cases. Patient reluctance to come forward for examination and investigation may be one reason for the few cases reported in this country to date. Dentists, general practitioners, and gastroenterologists working in areas where there is a large South Asian population, should be aware of this entity and take an active role in adopting preventive measures to reduce the incidence. Government legislation on betel importation and use if not even its banning should be considered.

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