Role of Iron Deficiency in Oral Submucous Fibrosis: An Initiating or Accelerating Factor

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ABSTRACT

To estimate the hemoglobin and serum iron levels in patients diagnosed with oral submucous fibrosis and to compare the values with that of the healthy subjects and with patients diagnosed of iron deficiency anemia. Patients reporting to the Department of Oral Medicine and Radiology, The Oxford Dental College, Hospital and Research Center, Bengaluru, who were clinically and histopathologically diagnosed with oral submucous fibrosis, were subjected for estimation of hemoglobin and serum iron levels by using Sahli’s method and Ferrene method respectively.

Hemoglobin and serum iron levels were low in patients with oral submucous fibrosis when compared with healthy control and a significant reduction in serum iron levels were found in comparison with anemic patients.

Keywords: Oral submucous fibrosis, Hemoglobin, Serum iron, Iron deficiency anemia.

INTRODUCTION

Oral submucous fibrosis (OSMF) is a well-established precancerous condition affecting the oral mucosa. Its literature dates back to as far as 2500 to 3000 BC when a renowned Indian physician Sushrutha mentioned about a condition—“Vidari” features which simulate OSMF.1 In 1966, Pindborg and Sirsat defined OSMF as an insidious chronic disease affecting any part of the oral cavity and sometimes the pharynx. Although occasionally preceded by and/or associated with vesicle formation, it is always associated with juxta-epithelial inflammatory reaction followed by a fibroelastic change of the lamina propria with epithelial atrophy leading to stiffness of the oral mucosa and causing trismus and inability to eat.2

The incidence of OSMF, chiefly in younger generation, is on the rise and is seen in high prevalence in India and South-East Asian countries. Etiological factors hypothesized to trigger the disease process include areca nut chewing, nutritional deficiencies, immunologic processes and genetic predisposition.3,4

Nutritional deficiency, primarily of iron and vitamins, is implicated in the etiology of OSMF. Iron is essential for the overall integrity and health of epithelia of digestive tract and its contribution to normal enzymatic functions. OSMF is also considered as an Asian version of sideropenic dysphagia, wherein chronic iron deficiency leads to mucosal susceptibility to irritants, such as chilies and areca nut products.5

Hemoglobin levels, in particular serum iron levels, are considered as biochemical indicators for nutritional assessment.6 Thus, the present study is undertaken to comprehend the association between OSMF and iron deficiency anemia by estimating the levels of hemoglobin and serum iron in patients diagnosed with oral submucous fibrosis and comparing the values with that of healthy subjects and further with the values of the patients diagnosed with iron deficiency anemia.

MATERIALS AND METHODS

All patients for the study were recruited amongst the outpatients attending the Department of Oral Medicine and Radiology, The Oxford Dental College, Hospital and Research Center, Bengaluru. Ethical clearance was obtained from the institutional committee, and informed consent was taken from the patients and healthy individuals who participated in the study.

The study group included 20 patients, clinically diagnosed with oral submucous fibrosis with no other systemic history. They were further subjected to histopathological confirmation. The study (OSMF) group was staged into stage I and stage II, as per the staging given by Pindborg.7

A control group included 10 healthy subjects whose age and sex were matched. Another 10 patients with iron deficiency anemia and without any history of areca nut chewing constituted the anemic group.

With due consideration of the aseptic precautions, 5 ml of fasting venous blood sample was collected and submitted for the estimation of hemoglobin and serum iron levels by using Sahli’s and Ferrene methods respectively.

Statistical analysis: The values obtained were statistically analyzed using Student’s t-test (two tailed, independent) to find the significance of study parameters on a continuous scale for intergroup analysis. Chi-square test was performed to test the homogeneity of samples based on the parameters and categorical scale between two groups. Analysis of variance (ANOVA) has been used to find the significance of the study.

RESULTS

The study (OSMF) group comprised of 20 cases of OSMF in age ranging from 18 to 48 years with a mean age of 28.85 ± 8.34 years. The maximum numbers of cases were between...
26 to 35 years. The OSMF group showed male predominance with 16 males and 4 females (Figs 1 and 2).

Mean values of hemoglobin and serum iron levels of control group were 14.23 ± 0.96 mg/dl and 129.90 ± 4.07 mcg/dl, whereas that of OSMF group were 12.96 ± 1.07 mg/dl and 51.56 ± 4.95 mcg/dl respectively. On comparison of OSMF group with the healthy group, OSMF group showed significantly lower levels of hemoglobin and serum iron with p < 0.001 (Figs 3 and 4).

Mean values of hemoglobin and serum iron levels in anemic group were 10.51 ± 1.31 mg/dl and 68.43 ± 24.69 mcg/dl, whereas those of OSMF group were 12.96 ± 1.07 mg/dl and 51.56 ± 4.65 mcg/dl respectively. On comparison between anemic and OSMF group, hemoglobin level was lower in anemic group but the serum iron level was significantly lower in the OSMF group, with p < 0.001 (Figs 3 and 4).

Interstage comparison showed a significantly lower hemoglobin and serum iron levels in stage II OSMF (Hb% = 11.67 ± 0.96 mg/dl/serum, Fe = 50.18 ± 4.77 mcg/dl) than stage I OSMF (Hb% = 12.32 ± 1.14 mg/dl/serum, Fe = 53.26 ± 4.89 mcg/dl). Value of p < 0.173 (Figs 5 and 6).

**DISCUSSION**

Oral submucous fibrosis is a chronic insidious and a disabling condition. Patients with OSMF have an assertive habit history of areca nut chewing, and a clear dose dependent relation is observed for both frequency and duration of chewing areca nut. The popularity and commercial availability of freeze dried areca nut products with tobacco in gutkha packets has been associated with a sharp increase in the frequency of OSMF.8

The mean age of the OSMF group in our study was 28.85 years, which is consistent with findings of 29.04 years by Katharia SK et al9 and 30 years by Maher R et al.10
A male proclivity is seen in the study group of 20 OSMF patients wherein 16 males and 4 females were present. Our findings of male proclivity are consistent with Chaturvedi VN and Marathe NG, Shah N et al, Raganathan K et al and Pindborg. A female predominance is seen in the anemia group, as iron deficiency anemia is very common in females because of chronic blood loss due to menstruation or in excessive demands as in pregnancy and lactation or poor nutrition intake.

The direct contact and continuous irritation from the various components of the areca nut products to the oral tissues produces a hypersensitivity reaction in the oral mucosa, thus initiating the disease. The period between initiation of the chewing habit and the development of clinical symptoms of OSMF varies tremendously ranging from a few months to several decades, depending on the type and duration of areca nut chewing habit. Soluble irritants, such as capsaicin present in chillies and alkaloids of areca nut, act as initiating factors causing a juxta-epithelial inflammatory reaction. Thus leading to burning sensation, vesiculation and ulceration of the oral mucosa, which render a phase for difficulty in consumption of the normal diet leading to poor nutrition. Deficiency of vitamin B complex, iron and other trace elements due to nutritional depletion could possibly initiate anemia and altered cell-mediated immunity, which in turn acts as a promoting factor to this pre-existing pathologic response of the epithelium. Such a hypersensitivity reaction in the oral mucosa, thus initiating the disease.

The present study conducted, shows significant lower levels of hemoglobin and serum iron on comparison with the values of the control group. Studies with similar results are reported by Anuradha CD and Shymala Devi, Rehana Maher, Sunali Khanna and Freny R Karjodkar and Lavina Taneja. Low levels of hemoglobin and serum iron are suggestive of iron deficiency anemia. Iron deficiency anemia in patients with OSMF could be related to the precancerous nature of this condition.

Cytochrome oxidase, an iron dependent enzyme, is required for the normal maturation of the epithelium. In iron deficiency state, levels of cytochrome oxidase are low, consequently leading to epithelial atrophy. An atrophic epithelium makes the oral mucosa vulnerable to the soluble irritants. Further lack of iron in tissues causes improper vascular channel formation resulting in decreased vascularity. This leads to derangement in the inflammatory-reparative response of the lamina propria resulting in defective healing and scarification. Thus, the cumulative effect of these initiating and promoting factors leads to further fibrosis, which is a hallmark of OSMF.

Fibrosis dictates that OSMF is basically a disorder of collagen metabolism. Hydroxypyroline is an amino acid found only in collagen, which is incorporated in the hydroxylated form. This hydroxylation reaction requires ferrous iron and ascorbic acid. Utilization of iron, for the hydroxylation of proline and lysine, leads to decreased serum iron level. In OSMF patients, there is an increase in the production of highly crosslinked insoluble collagen type I, loss of more soluble procollagen type III and collagen type VI. The crosslinking of collagen due to the upregulation of lysyl oxidase, plays a crucial role in the development and progression of the condition from stage I to stage II. From the above discussion, it is evident that a suggestively significant lower level of hemoglobin and serum iron can be accepted in stage II OSMF patients than in stage I, concluding that as disease progresses, serum iron levels also depletes.

Serum iron content can be a predictor for the progression of the condition. There appears an association between serum iron content and oral carcinogenesis. It is well-documented that patients with severe iron deficiency condition, known as siderophagic dysphagia or Plummer-Vinson syndrome, are at a higher risk of developing oral carcinoma, postcricoidal carcinoma and esophageal carcinoma. OSMF is also known as Asian version of ‘siderophagic dysphagia’. Though OSMF is a clinically benign condition, it is a potentially malignant disease having a malignant transformation rate of 5 to 13%. The present study, which also included the comparison of serum iron levels of OSMF patients versus the anemic patients without the history of areca nut chewing habit, showed lower hemoglobin level in anemic group but a significant reduction in serum iron level was observed in the OSMF group.

Although OSMF and iron deficiency anemia exists as separate conditions, the clinical findings of OSMF mimic those of iron deficiency anemia, which includes blanching, burning sensation and dysphagia. Histologically in both the conditions, due to a qualitative and quantitative defect in the oxygen and nutrient perfusion of the lamina propria and the overlying mucous membrane, epithelial atrophy occurs. The effect of soluble irritants on the atrophic epithelium, which ensues in due course leads to malignancy (Fig. 7). Thus, this unclear line of demarcation between both these precancerous conditions still persists, which calls upon for further extensive studies to comprehend the correlation between OSMF and iron deficiency anemia as well as the validation of serum iron levels in various stages of OSMF, as an indicator of malignant transformation.

CONCLUSIONS

The present study emphasizes on the serum iron assessment for patients with oral submucous fibrosis. Determining iron status is a part of biochemical assessment, which may be of proactive intervention for high-risk groups. It is suggested that the biochemical assessment of oral precancerous conditions may help in early diagnosis and/or prognosis. It also serves in predicting the malignant potential, especially in high-risk groups.

It is also of prime importance that iron therapy should be instituted concomitantly with the initial diagnosis along with a proper balanced diet, as a part of the overall treatment of oral submucous fibrosis with other modes of treatment. This helps to cease the further progression of the condition.
REFERENCES