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Clinical And Hematological Profile Of Patients With Oral Submucous Fibrosis– A Cross Sectional Study In A Tertiary Care Hospital, Mandya.

Dr Ravi D[1], Dr Balaji NK[2], Dr Shreya Sinha[3]
(Department Of Otorhinolaryngology, Mandya Institute Of Medical Sciences, India)
(Department Of Otorhinolaryngology, Mandya Institute Of Medical Sciences, India)
(Department Of Otorhinolaryngology, Mandya Institute Of Medical Sciences, India)

Abstract
Background: *A significant proportion of oral squamous cell carcinomas (OSCC) develop from premalignant lesions such as leukoplakia and conditions such as oral submucous fibrosis(OSMF). Deficiency of iron, Vitamin B-12, and folate can affect the integrity of the oral mucosa. Significant hematological abnormalities have been reported in OSMF, including an increased blood sedimentation rate, and a decrease in serum iron and an increase in total iron binding capacity. Therefore, this study is aimed at estimating hematological parameters in OSMF patients and to analyze their association with different grades of OSMF.*
Materials and methods: *A cross sectional study was conducted in the otorhinolaryngology out-patient department. 60 patients diagnosed with OSMF were included in the study. Demographic data collected, detailed history regarding symptoms taken, clinical examination performed and patients were categorised according to clinical and functional staging of OSMF. Blood samples sent for complete hemogram analysis and estimation of serum vitamin B12 levels.*
Results: *Average age of cases was 32.8 years, with male-female ratio of 5:1. Burning sensation and inability to open mouth were the chief complaints. In all cases changes in colour of buccal mucosa and palpable fibrous bands with trismus were present. The maximum patients were seen in grade II (46.6%). The mean value of hemoglobin was 10.94±2.95gm/dl, and serum vitamin B12 was 220±45.5pg/ml.*
Conclusion: *It was concluded that there is a significant association between decreased hemoglobin and serum vitamin B12 levels and OSMF. Therapeutic substitution of vitamin B12 and anemia correction may be recommended in the management of OSMF.*
Keywords: *premalignant; submucous fibrosis; malignancy; anemia; trismus*

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I. Introduction

Oral Cancer accounts approximately 40% of all cancers in the Indian subcontinent.[1] A significant proportion of oral squamous cell carcinomas (OSCC) develop from premalignant lesions such as leukoplakia and conditions such as oral submucous fibrosis(OSMF).[2] OSMF is defined as insidious chronic disease affecting any part of oral cavity and sometimes pharynx. Although occasionally preceded by and/or associated with vesicle formation, always associated with juxtaepithelial inflammatory reaction followed by fibro elastic change of lamina propria with epithelial atrophy leading to stiffness of oral mucosa and causing trismus and inability to eat.[3] In recent years, OSMF has received considerable attention as a precursor to cancer and occurs in younger age group individuals.[4] It's reported risk of malignant transformation varies from 7 to 13%. [5]

Habit of chewing areca nut is the major etiological factor of OSMF. It's extract acts as a potent stimulator for collagen synthesis in human fibroblasts culture leading to excessive accumulation of collagen, leading to fibrosis.[6] High levels of copper in areca nuts, a major etiological factor in OSMF plays an initiating role in stimulation of fibrinogenesis by up-regulation of lysyl oxidase and thereby causing inhibition of degradation of collagen and causing its accumulation thereby causing OSMF. The high serum copper levels may also lead to generation of high levels of free radicals by metal-catalyzed Haber-Weiss reaction and this can be one of the reasons for the carcinogenesis in tobacco and areca nut users.[7]

Hemoglobin levels, in particular serum iron levels, are considered as biochemical indicators for nutritional assessment.[8] Deficiency of iron, Vitamin B-12, and folate can affect the integrity of the oral mucosa. Significant hematological abnormalities have been reported in OSMF, including an increased blood sedimentation rate, and a decrease in serum iron and an increase in total iron binding capacity. [9]

II. Materials And Methods

This was a cross sectional study conducted in the Out-patient Department, Department of Otorhinolaryngology, Mandya Institute of Medical Sciences, which was initiated after obtaining approval from the Institutional Ethics Committee. The study was conducted over a period of six months (October 2023 to March 2024), on 60 subjects.

Study Design: cross sectional study

Study Location: Out-patient Department, Department of Otorhinolaryngology, Mandya Institute of Medical Sciences, Mandya, Karnataka.

Study Duration: October 2023 to March 2024

Sample Size: 60 patients

Sample size calculation: The formula used for sample size calculation is $N = Z^2 \times p \times (1-p) / d^2$ here, Z = standard normal variate (1.96), P = prevelance of decreased hemoglobin in patients with OSMF = 86% [13], D = relative error (10% of P), 10% of 86 = 8.6, N= 1.96 x 1.96 x 86 x 14/ 8.6 x 8.6 = 62.54. Rounded off to 63. As only 60 patients fulfilling the inclusion and exclusion criteria attended the out patient department, hence a sample size of 60 patients was taken.

Subjects and selection method: Consecutive enrolment till the sample size was met.

Inclusion Criteria:
1) Patients with clinically diagnosed oral submucous fibrosis with presence of burning sensation in mouth, inability to consume spices, stiffness of buccal mucosa, vesicle formation, ulceration, restricted mouth opening and blanching of oral mucosa, aged between 18-60 years attending out- patient department, Department of Otorhinolaryngology, MIMS, Mandya.
2) Patients willing to give written informed consent.

Exclusion Criteria:
1) Patients with any other precancerous lesions or conditions other than OSMF.
2) Patients suffering from any systemic diseases like diabetes, hypertension, cardiac diseases, renal diseases, liver diseases and other malignancies.
3) Patients who are taking antioxidants/multivitamin preparations.

Procedure methodology

The demographic parameters like age, gender, occupation, socio economic status were recorded on a proforma. A detailed history regarding symptoms were taken, and clinical examination was performed and recorded. Diagnosis was made on clinical basis and patients were categorized according to clinical and functional staging of OSMF.

Clinicopathological staging of OSMF given by Passi et al (2017)

Grading/Staging	Clinical grading	Functional grading
Grade 1	Involvement of < 1/3rd of the oral cavity, mild blanching, burning sensation, recurrent ulceration and stomatitis, dryness of mouth	Mouth opening upto 35mm
Grade 2	Involvement of 1/3rd to 2/3rd of the oral cavity, blanching, mottled and marble-like appearance, fibrotic bands palpable and involvement of soft palate and premolar area	Mouth opening 25-35mm, cheek flexibility reduced by 33%
Grade 3	Involvement of >2/3rd of oral cavity, severe blanching, broad thick palpable fibrous bands at cheeks and lips and rigid mucosa, depapillated tongue and restricted tongue movement, shrunken bud like uvula, floor of mouth involvement and lymphadenopathy	Mouth opening 15-25mm, cheek flexibility reduced by 66%
Grade 4	Changes like leukoplakia, erythroplakia, ulcerating or a suspicious malignant lesion	Mouth opening <15mm or nil

Blood samples were collected and sent for complete hemogram analysis, estimation of serum ferritin and vitamin B12 levels.

Statistical analysis

Data was fed into Microsoft excel worksheet and analyzed using SPSS (software package for social sciences) software. Descriptive statistical tests like proportion, percentage, mean and standard deviation were used. Inferential statistical test like Anova was done to know the association between levels of hematological parameters, serum ferritin and serum vitamin B12 with grade of OSMF. P-value of <0.05 was considered as significant.

III. Results

Patients included in the study were in the age group from 24 to 62 years, with average age being 32.8 years. Male-female ratio was 5:1. Difficult mouth opening and burning sensation were the chief complaints in most patients. Trismus and fibrotic bands were the most common signs noted.

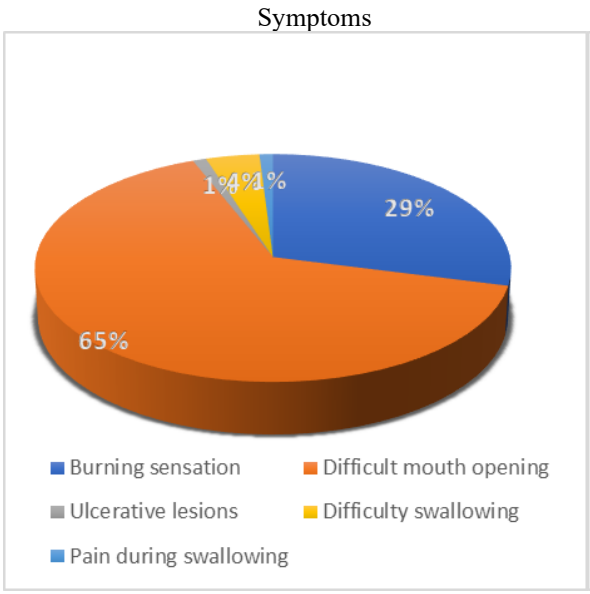

Fig 4a

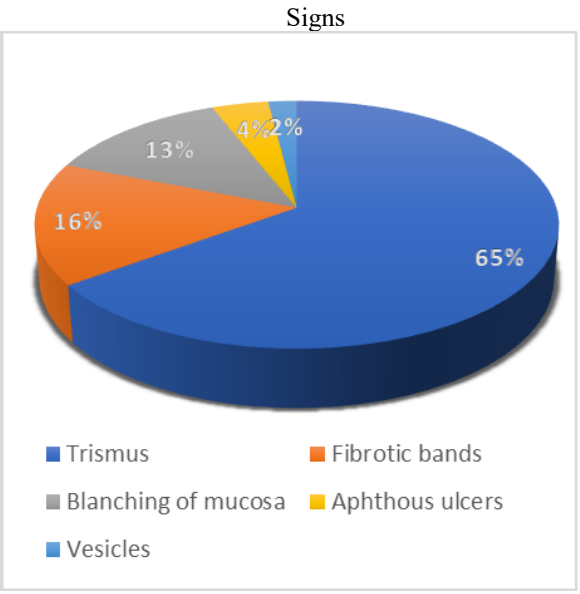

Fig 4b

The most common symptom was difficult mouth opening in 65% of patients, followed by burning sensation in oral cavity in 29% of patients, followed by difficulty swallowing (4%). Other symptoms included pain during swallowing and ulcerative lesions. Most common sign was trismus in 65% of patients, followed by fibrotic bands in 16%. Other signs noted were blanching of mucosa, aphthous ulcers and vesicles (Fig 4a and 4b).

History of areca nut chewing or other forms of tobacco chewing was present in all patients. Maximum number of patients were seen in grade II (46.6%), followed by grade I (31.6%).

Grade of OSMF	No. of patients (out of 60)	Percentage (%)
Grade 1	19	31.6
Grade 2	28	46.6
Grade 3	9	15
Grade 4	4	6.6

Fig 5: Distribution of patients into grades of OSMF

Severity of trismus measured in terms of mouth opening in millimeter (mm) was found to be most severe in patients with grade 4 OSMF (mean 12.4 mm mouth opening), followed by grade 3 (mean 19.1 mm), followed by grade 2 (mean 26.5 mm), followed by grade 1 (mean 36.2 mm).

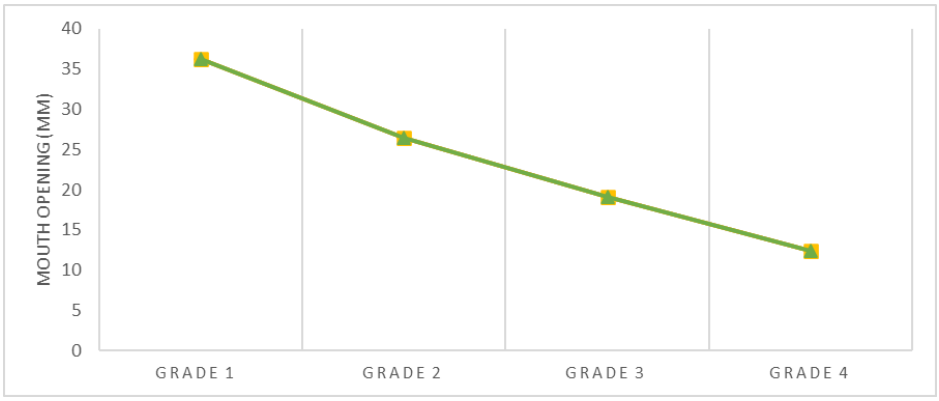

Fig 6: Graph depicting severity of trismus (in terms of mouth opening in mm) among different grades of OSMF

Mean value of hemoglobin was 10.94±2.95gm/dL, which was significantly low (p<0.001).

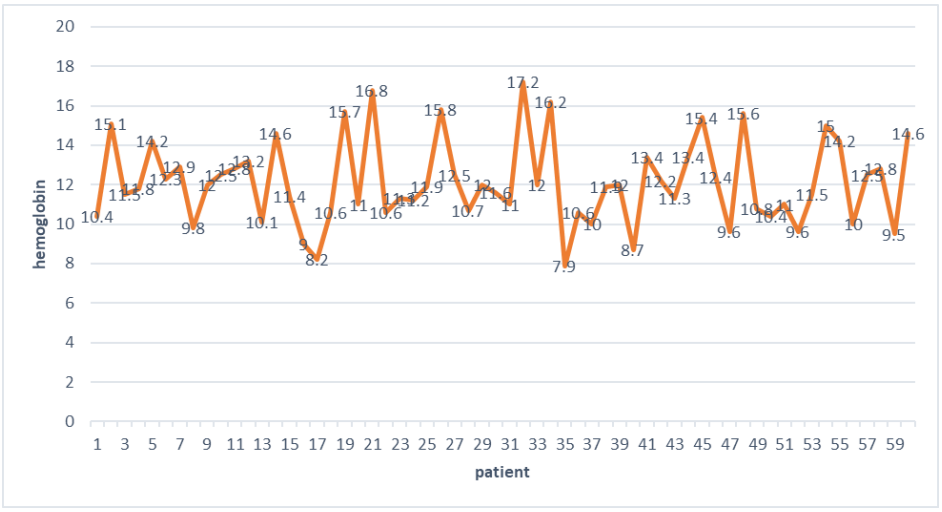

Fig 7: Graph depicting Hemoglobin levels of study subjects

Mean value of serum vitamin B12 was 220±45.5pg/mL, which was significantly low (p<0.001). Normal values being 187-883 pg/ml.

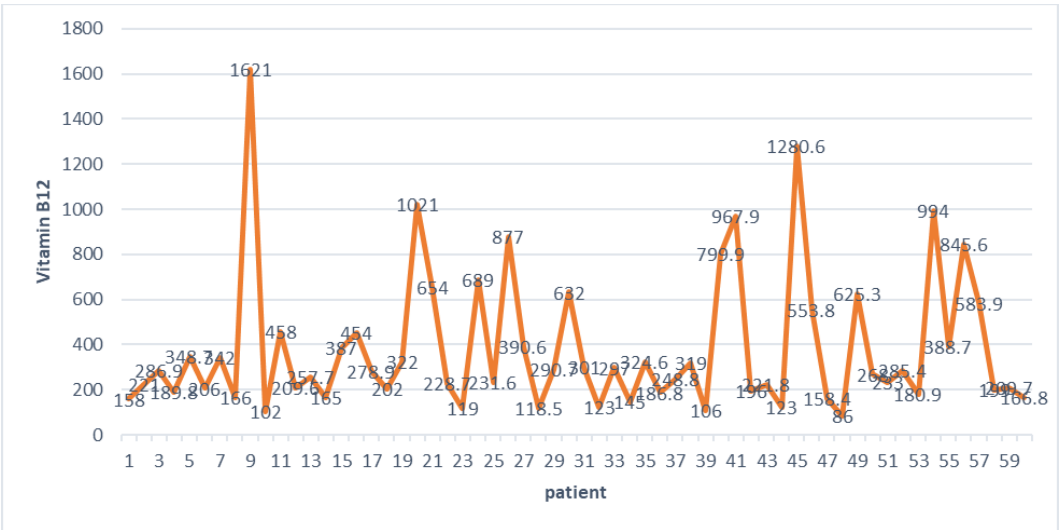

Fig 8: Graph depicting serum Vitamin B12 levels of study subjects

Mean value of serum ferritin was 79.6ng/mL, which was significantly low (p<0.001). Normal value being 21.81-274.66ng/mL in males, and 4.63-204ng/mL in females.

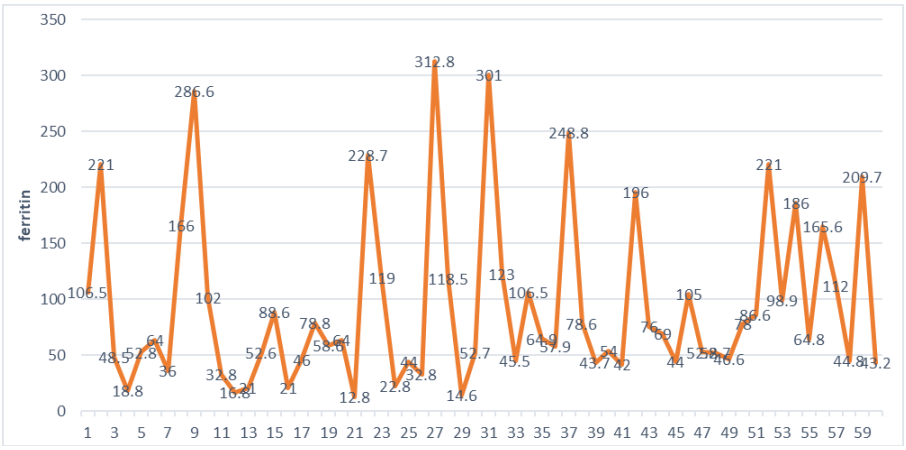

Fig 9: Graph depicting serum Ferritin levels of study subject

Among patients with grade 1 OSMF (19 patients), mean hemoglobin levels were noted to be 12.35 gm/dL, mean serum vitamin B12 levels were 268.8 pg/mL, and mean serum ferritin levels were 126.5 ng/mL. Among patients with grade 2 OSMF (28 patients), mean hemoglobin levels were noted to be 10.96 gm/dL, mean serum vitamin B12 levels were 220.4 pg/mL, and mean serum ferritin levels were 78.6 ng/mL. Among patients with grade 3 OSMF (9 patients), mean hemoglobin levels were noted to be 10.54 gm/dL, mean serum vitamin B12 levels were 201.5 pg/mL, and mean serum ferritin levels were 67.7 ng/mL. Among patients with grade 4 OSMF (4 patients), mean hemoglobin levels were noted to be 9.87 gm/dL, mean serum vitamin B12 levels were 190.8 pg/mL, and mean serum ferritin levels were 46.2 ng/mL. Hence, with increasing grades of OSMF, the mean values of hematological parameters were noted to be decreasing.

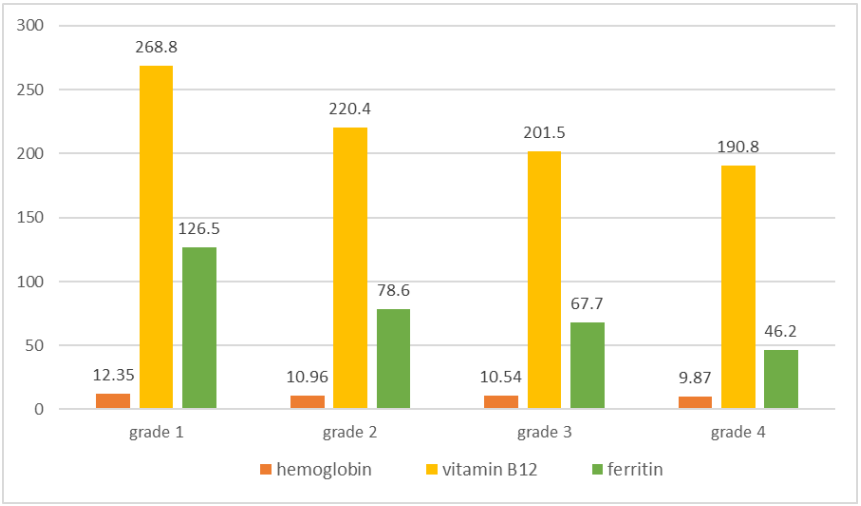

Fig 10: Graph depicting levels of hematological parameters in different grades of OSMF

IV. Discussion

The clinical profile and hematological parameters of 60 clinically diagnosed cases of oral submucous fibrosis has been presented above. In the present study, average age of patients was 32.8 years. Males predominated females in the ratio of 5:1. Difficult mouth opening and burning sensation were the chief complaints in most patients. Trismus and fibrotic bands were the most common signs noted. History of areca nut chewing or other forms of tobacco chewing was present in all patients. Mean value of hemoglobin was 10.94±2.95gm/dL, which was significantly low ($p<0.001$). Mean value of serum vitamin B12 was 220±45.5pg/mL, and mean value of serum ferritin was 79.6ng/mL. With increasing grades of OSMF, mean values of hematological parameters were found to be decreasing. Our results were in correlation with previous studies which also recorded decreased levels of hematological parameters in such patients.

Various case control studies conducted by Bharadwaj D et al, Dinkar A et al , Satoskar SA et al, Desai SR et al, Karthik R et al , Nair P et al, Gharote P et al, Agarwal K et al, Bhat R et al, Rajaram K et al in Goa and Bhopal during 2011 to 2016 shows the mean value of haemoglobin of control group was 13.83±1.39g/dl whereas that of OSMF group was 10.94±2.95gm/dl, and serum iron levels of control group were 140.13 mcg/dL, whereas

those of OSMF group were 55.53 mcg/dL. On comparison of the OSMF group with the healthy group, OSMF group showed significantly lower levels of haemoglobin and serum iron with $p< 0.001$. [10,12] A cross sectional study conducted by Harini et al in Chennai during 2021 shows the mean iron value in OSMF patients is 195.89µg/dL and the mean B12 value in OSMF patients is 95.45µg/dL, which is significantly lower than the normal range. [11]

Oral submucous fibrosis does not regress with habit cessation. But if identified in early stages its progression can be stopped by different treatment modalities including behavioral therapy for cessation of habit, physiotherapy includes blowing, heat therapy and forceful mouth opening exercises, local corticosteroids injection along with hyaluronidase, collagenase, interferon gamma, antioxidants includes phytochemical lycopene, combined therapy of peripheral vasodilators, vitamin B complex, placental extracts, local and systemic steroids and physiotherapy. Surgical management includes surgical splitting or excision of fibrous bands which may improve mouth opening and mobility in later stages of disease. [4]

V. Conclusion

It was concluded that there is a significant association between reduced hemoglobin, reduced serum ferritin and serum vitamin B12 levels and OSMF. With increasing grades of OSMF, mean values of hematological parameters were found to be decreasing. On the basis of these observations, it seems possible that the chemical, thermal and/or mechanical factors associated with the use of tobacco may act in conjunction with the vitamin deficiencies and anemia to lead to the development of oral submucous fibrosis.

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