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ESOPHAGEAL DYSPLASIA IN HIGH RISK GROUP AND SIGNIFICANCE OF AgNOR IN ESOPHAGEAL DYSPLASIA

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ABSTRACT

Study of prevalence of various grades of dysplasia in the middle third of esophagus in asymptomatic individuals with high risk factors. AgNOR staining as a proliferation marker and prognostic indicator. The odds ratio for various risk factors were calculated.There was increase in AgNOR count with increasing dysplasia. Alcohol and smoking either alone or in combination with a duration of more than 10 years is likely to predispose an individual to dysplasia. Dysplasia is more prevalent in high risk group. AgNOR study simple, inexpensive and reliable proliferation marker.

KEYWORDS : Dysplasia, Risk Factor, AgNOR, Proliferative Marker

Esophageal cancer is the sixth most common fatal cancer in the world. The five year survival rate is among the lowest for all cases (14%)(Wang G-Q et al, 2005), the main reason being cancer of the esophagus becomes symptomatic at an advanced phase with a late diagnosis when the tumor is already incurable. Hence for early detection of esophageal malignancies, the susceptible population should be subjected to screening to identify any precancerous condition. Squamous dysplasia and squamous cell carcinoma in situ are known to be precursor lesions of frank esophageal malignancy. All grades of squamous dysplasia and carcinoma in situ are associated with a significantly increased risk of developing esophageal squamous cell carcinoma. Increasing grade of dysplasia are associated with dramatically increased risk(Ohta M, et al, 1986). If these dysplastic lesions can be identified in the high risk population this dreadful condition can be dealt with more effectively(Takiyama W, et al, 1989). By studying this high risk group for the development of dysplasia a causal association can be established which can be used as a basis for devising effective screening protocols to pick up cases at an early stage. Once dysplasia is documented it is classified as mild, moderate or severe based on the extent to which the immature cells replace the normal epithelium. Mild dysplasia might be re-evaluated periodically or treated by chemo prevention. Moderate dysplasia may be followed more closely or treated by focal endoscopic therapy. Severe dysplasia and carcinoma in situ should be treated by endoscopic mucosal resection. The high risk group has been defined as individuals with habits like alcohol consumption, smoking, tobacco chewing and with intake of hot beverages like coffee or tea either alone or in combination and who are more prone to develop dysplasia. Esophageal biopsies of asymptomatic individuals who belong to high risk group are examined for the presence of dysplasia and the findings are compared with age matched subjects without the risk factors. And correlation of duration of risk factor with the occurrence of dysplasia is also evaluated. Further the significance of AgNOR study in dysplasia of esophagus is also evaluated.

MATERIALS AND METHODS

121 consecutive male patients above 25 years of age who attended the department of Medical GastroEnterology, Government Stanley Medical College and Hospital for upper Gastro-Intestinal endoscopy with complaints of dyspepsia without alarm between July 2004 and May 2006 constituted the study group. Adequate material for study was obtained only in 79 cases. Information obtained included demographic data, occupation, literacy, socio- economic status and habits like smoking, alcohol use, tobacco chewing, use of nasal snuff and use of beverages like hot tea or coffee and were noted in pre-structured proforma and recorded by a single person. Endoscopic biopsy specimens were obtained from the anterior and posterior wall of the middle third of the esophagus. Haematoxylin and Eosin stained sections were studied for the presence or absence of dysplasia and dysplastic cases were further graded into mild, moderate and severe dysplasia, based on the thickness of dysplastic

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epithelium. Based on the histopathological report, cases and controls were segregated.

A case was defined as one with dysplasia on histopathology irrespective of risk factors. A control was defined as one with no dysplasia on histopathology irrespective of the risk factors.

A further study was done to assess the proliferative activity of dysplastic cells by silver staining for nucleolar organizing regions and AgNOR count was done by manual counting using oil immersion objective and the results were tabulated. Total of 100 cells were studied for Intra-nuclear silver stained dots in each section and AgNOR score was calculated. Odds ratio which indicates the strength of association between risk factors and outcome was calculated for each risk factor using standard statistical formulas and the results were analysed.

RESULTS

Out of 79 biopsies studied, the results obtained were as follows.

Table 1 : Results of Biopsies Studied

Total number of biopsies studied	79
Biopsies showing dysplasia	40
Biopsies reported as normal	39
Mild dysplasia	21
Moderate dysplasia	12
Severe dysplasia	7

Figure of Mild, Moderate and Severe dysplasia are shown in Figure -3, 5 and 7respectively table 1 .

Table 2 : Number of Cases Exposed To Risk Factors

Alcohol	28
Smoking	28
Alcohol & Smoking	23
Other Tobacco Products	9
Beverages	28

Table 3 : Number of Controls Exposed To Risk Factors

Alcohol	4
Smoking	8
Alcohol & Smoking	3
Other Tobacco Products	9
Beverages	34

Mean age of cases: 44.64 ± 9.65
Mean age of controls: 43.35 ± 9.70

Odds ratio which is defined as the measure of the strength of association between the risk factors and outcome was calculated in each category (Table 2 and 3).

Table 4 : Odds Ratio in Different Risk Factors

Risk Factor	Odds Ratio
Alcohol	22.90
Smoking	10.10
Alcohol and Smoking	17.7
Other tobacco products	1.03
Beverages	0.45

From this data, the strength of association is very significant for alcohol and smoking as individual factor and also in combination (Table 4).

Table 5 : Alcohol-Correlation of Duration of Exposure with Dysplasia

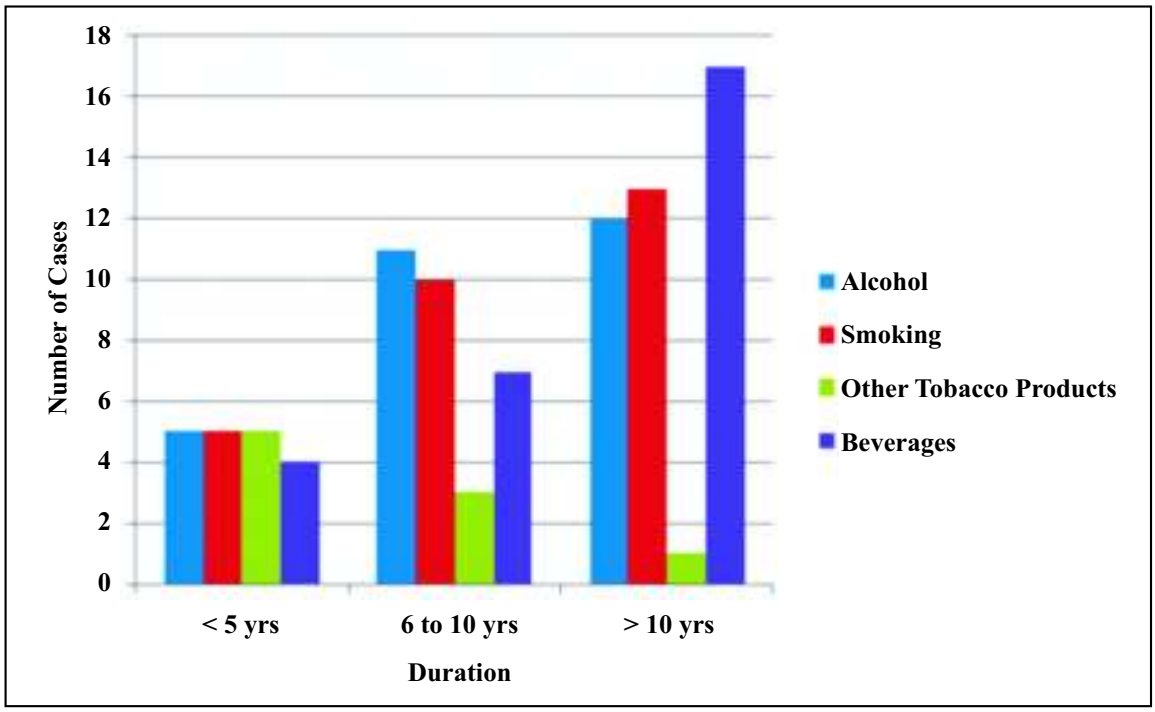
Duration of exposure	Dysplasia	% of Cases
< 5 years	5	17.5%
6 – 10 years	11	39.2%
> 10 years	12	42.9%

Table 6 : Smoking–Correlation of Duration of Exposure with Dysplasia

Duration of exposure	Dysplasia	% of Cases
< 5 years	5	17.8%
6 – 10 years	10	35.7%
> 10 years	13	46.4%

Among the alcohol users when duration was more than 5 years,risk was found to be 39.2% and with duration of more than 10 years, risk was found to be 42.9% (Table 5).

In smokers when duration was more than 5 years , risk was found to be 35.5% and with duration of more than 10 years, risk was found to be 46.4% (Table 6).



Graph 1 : Correlation of Duration of Risk Factor With Dysplasia Results Were Obtained

Alcohol Includes:

1. High Spirit 2. Toddy / Beer 3. Both

Smoking Includes:

1. Cigarettes 2. Beedi 3. Both

Other Tobacco Product Includes:

1. Snuff 2. Beetel nut 3. Both

Beverages Includes:

1. Coffee 2. Tea 3. Both

Table 7 : Results of AgNOR Study

HPE Report	Number of Cases	Mean ± Std. Deviation
Normal	29	2.28 ± 0.76
Mild Dysplasia	18	2.43± 0.39
Moderate Dysplasia	15	3.0073± 0.63
Severe Dysplasia	6	3.4885± 0.84
Malignancy	8	4.65± 0.47

The figures of AgNOR study and their corresponding H&E pictures are as given in Figure 1 - 10.

DISCUSSION

In India, squamous cell carcinoma of the esophagus is the third most common malignancy in men and fourth most common malignancy in women. In men, majority of the cases occur in the 6th and 7th decades. It is commonly seen in lower socio- economic group and is more prevalent in those who smoke,drink alcohol and use pan or tobacco. There is an increase in the incidence of malignancies of 2.8 and 2.5 fold, seen in smokers and tobacco chewers respectively. The risk with alcohol is found to be increased three fold, which is significantly higher than that was reported earlier from other centres in our country. A strong association is found between cancer of the esophagus and risk factors like alcohol, smoking and betel nut chewing among south Indian patients.

An attempt was made here to ascertain the association of these risk factors to the development of dysplasia in the middle third of the esophagus, the segment where carcinoma of the esophagus frequently occurs.

On analysing the results it was found that the high risk group is more prone to develop dysplasia of the esophagus compared to the low risk group without these risk factors. The finding in this study correlates with the previous studies implicating smoking and alcohol in the

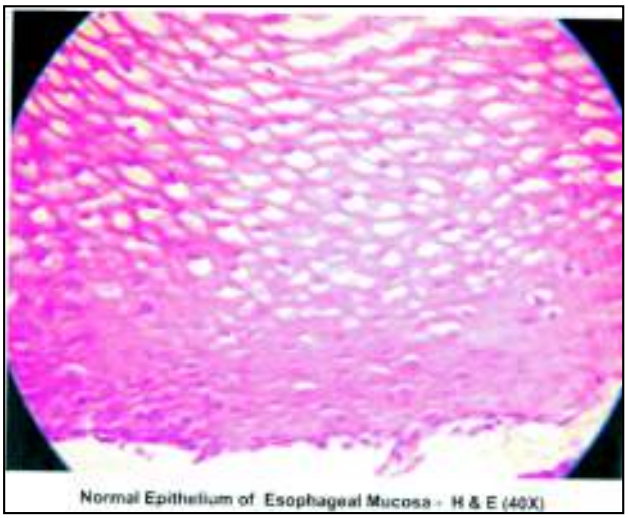


Figure 1 : Normal Squamous Epithelium - Esophagus

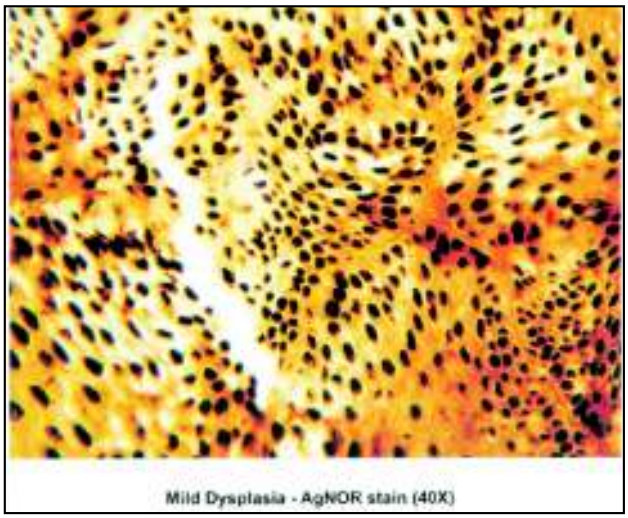


Figure 4: Mild Dysplasia AgNOR Stain

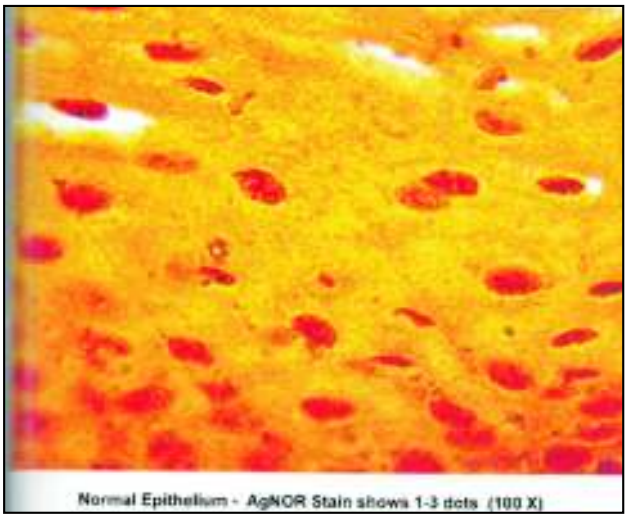


Figure 2 : Normal Epithelium AgNOR Stain

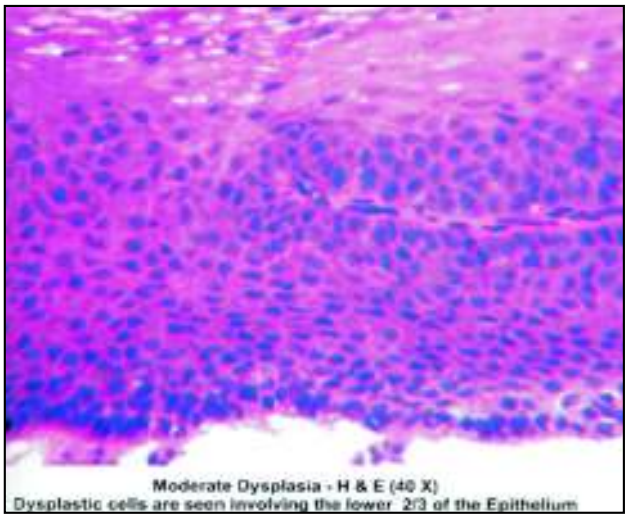


Figure 5 : Moderate Dysplasia

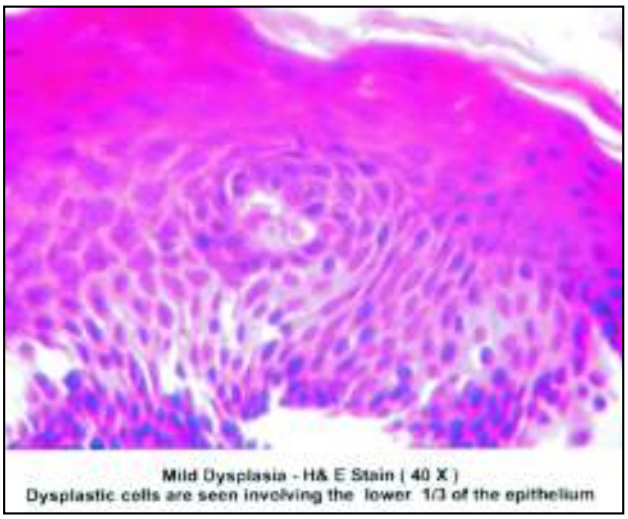


Figure 3 : Mild Dysplasia

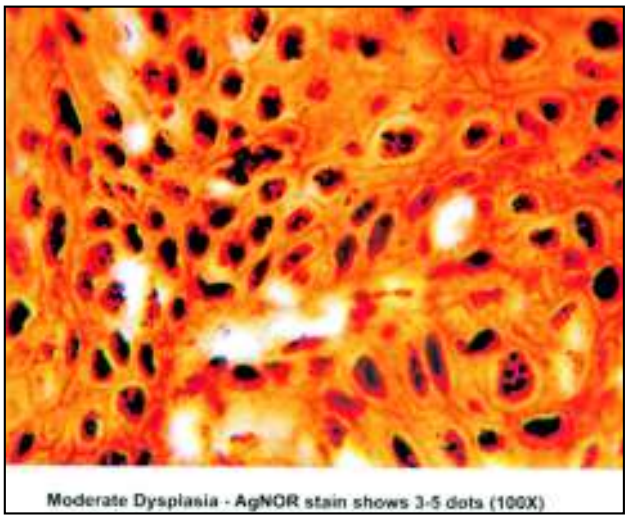


Figure 6 : Moderate Dysplasia AgNOR Stain

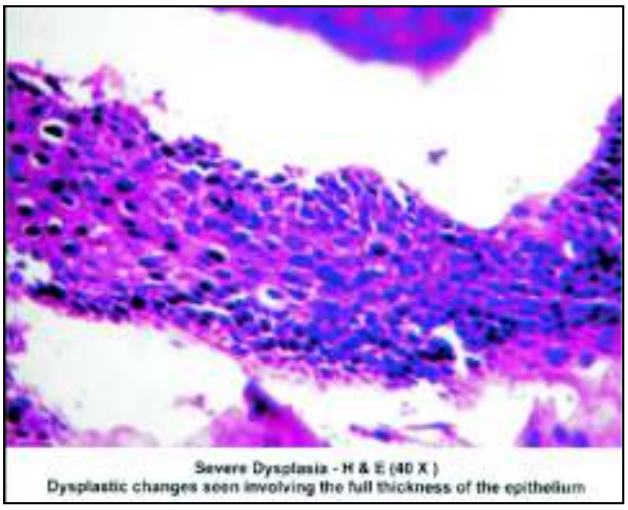


Figure 7 : Severe Dysplasia

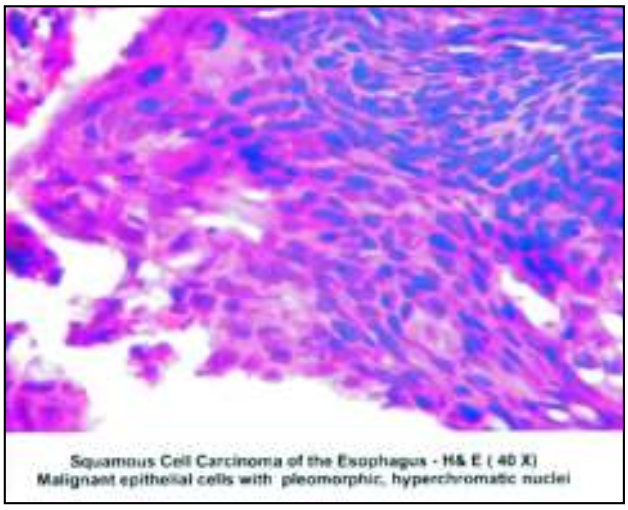


Figure 9 : Squamous Cell Carcinoma

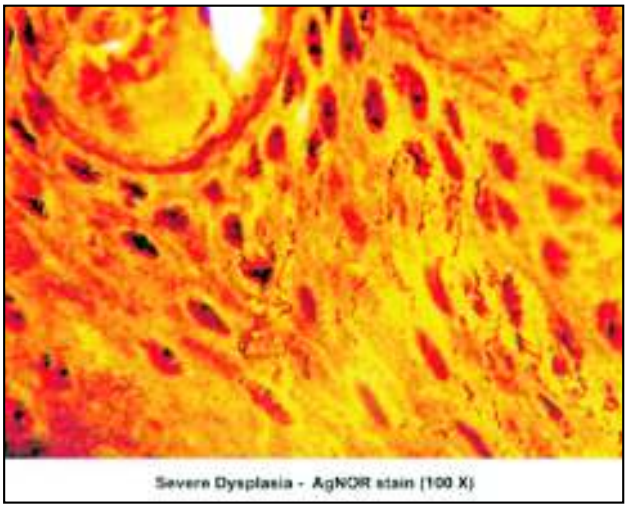


Figure 8 : Severe Dysplasia AgNOR Stain

Figure 10 : Squamous Cell Carcinoma AgNOR Stain

causation of squamous cell carcinoma of the esophagus and is a strong indicator that the susceptible population should be subjected to vigorous screening programmes to detect early lesions.

When the dysplastic cases were studied for subtyping into mild, moderate and severe dysplasia it was observed that in the same case different areas showed different grades of dysplasia and this is a clear indication of the natural progression of increasing grades of dysplasia similar to other dysplasia carcinoma sequences like carcinoma of the cervix.

Some of the individuals showed dysplastic changes without history of exposure to any of the risk factors included in this study. It implies that there could be other agents or risk factors responsible for the development of dysplasia in such cases and it underscores the need for more such studies to unravel the unknown culprits.

The study of AgNORs has recently received increased attention because of claims that counting of AgNORs gives a score which is representative of the level of proliferative activity of the sample studied.

It was found that AgNOR counts are of definite value in grading of dysplasia and when considered along with other proliferation markers it could be of even more significance. The application of AgNOR as a potential prognostic indicator or predictor of optimal treatment protocol may require long term clinical follow up. It was observed that the difference in AgNOR values as seen in Table : 7, in normal epithelium and dysplasia is very significant and the AgNOR values in malignant epithelium

was very much increased compared to normal epithelium. However, when the values for mild, moderate and severe dysplasia were compared as separate groups, the difference between normal epithelium and mild dysplasia was not marked. But moderate and severe dysplasia showed significant difference in values as compared to normal epithelium.

The marked difference between mAgNOR of normal epithelium and malignant epithelium signifies the value of AgNORs as a proliferative marker and its utility in dysplasia as a screening tool. When it is used in combination with other proliferative markers it will definitely give very significant information about the malignant or premalignant potential of the sample studied. AgNOR study which is simple and inexpensive procedure can be used as a valuable proliferation marker and prognostic indicator.

CONCLUSION

Study has attempted at correlation of risk factors and their duration with onset of dysplasia in the esophagus. Alcohol and smoking (either alone or in combination), with a duration of more than 10 years is likely to predispose an individual to dysplasia. Conclusions on beverages needs further validation. Dysplasia is more prevalent in the high risk group as compared to low risk group. Dysplasia in person in the low risk group may be due to other risk factors not included in the study (18%). AgNOR study is a simple, inexpensive and reliable proliferation marker in esophageal dysplasia.

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