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Mucin Histochemical Features of Esophageal Adenocarcinoma as a Predictor of Prognostic Outcome: A Clinicopathological and Histochemical Study

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Abstract

Aim: *The aim of this study is to evaluate the various clinicopathological factors and correlate with mucin histochemical features in patients with the adenocarcinoma of the esophagus, all of whom underwent total esophagectomy.*

Material & Method: *Data of a total of forty five patients with adenocarcinoma of the esophagus, all patients having undertaken total esophagectomy at Department of Surgery, AIIMS, New Delhi in between January 1980 and December 1995, were retrospectively analysed for study. All these patients were divided into two groups, cases (21) and controls (24); depending on the outcome of interest at 24 months (i.e. death or survival); controls being the patients, who survived for 24 months. Patients were evaluated with reference to clinicopathological variables and mucin histochemistry. Sections were stained by the Alcian Blue / Periodic Acid Schiff & High iron Diamine Alcian Blue technique to identify neutral mucin and acid mucin (sialomucin and sulphomucin).*

Results: *It is apparent from this study, that the well-known clinicopathological variables like age, sex, consumption of tobacco &alcohol, symptoms, location, differentiation, stage, that affect survival were in no way different in cases and controls. Therefore, role of mucin histochemical characteristics were explored and it was found that presence of mucin (acid / neutral) in any location (intracellular / extracellular) may be associated with poor prognosis. Again among the extracellular acid mucins, sulphomucin is almost associated with worse prognosis.*

Conclusion: *Well known clinicopathological variable that affect poor survival were analysed retrospectively, for adenocarcinoma esophagus who underwent esophagectomy; 24 months being taken as the outcome of interest (death or survival); control were the patients who survived for 24 months. No statistically significant difference was found among clinicopathological variables. However, mucin histochemical characteristics and amongst these extracellular acid mucin; sulphomucin is almost always associated with poor prognosis.*

Introduction

Esophageal cancer is a particularly virulent malignancy associated with poor long term survival. As per GLOBOCAN[1] 2018 data, esophageal cancer ranks 6th in India, both in terms of incidence (52,396 new cases) and mortality (46,504 deaths). In USA, the scenario is a bit better, with esophageal cancer ranking 20th in incidence and 11th in mortality.

Presently the prognosis of adenocarcinoma of esophagus depends essentially on grade and stage of the tumors& operability. The availability of a specific tumor marker for cancer of esophagus, would have been helpful, but to date no such tumor markers, with the necessary degree of accuracy has been identified. Mucin histochemical characteristics are also being explored. A predominance of sulfated mucin in the columnar cells (but not the Goblet cells) of Barrett's specialized metaplastic epithelium has been postulated to indicate an increased risk of adenocarcinoma. Jass et al extended these observations to Barrett's esophagus and found that a predominance of sulphomucin in Barrett's esophagus was associated with well differentiated, but not with poorly differentiated adenocarcinoma. Jass postulated that sulphomucin staining might permit identification of patients at risk for developing esophageal adenocarcinoma, complicating Barrett's esophagus.

Therefore, this study intends to correlate prognosis with clinicopathological characteristics of esophageal adenocarcinoma and to evaluate usefulness of mucin histochemistry in the assessment of grading, staging and prognosis of esophageal adenocarcinoma.

Regarding site of tumor, to avoid confusion tumors of the lower third are further sub divided into the following three regions: 1) True lower esophageal tumor without involvement of stomach either grossly or microscopically. 2) Gastro esophageal (GE) junction tumors with less than 50% of the tumor volume involving proximal stomach and 3) True gastric cancer with more than 50% of the tumor volume involving the stomach.

In our institute, only the first two groups are regarded true adenocarcinoma of the esophagus and gastro esophageal junction. The Third group reflects locally advanced gastric cancers, as in the first two, they almost never have signet cell features, which is very common in gastric adenocarcinoma (Griesenger, 1992)[2].

Columnar epithelium lined (Barrett's) esophagus needs mention in this context. Barrett (1950) claimed that the ulcer arose in the stomach & interpreted this finding as congenitally short esophagus with secondary reaction in proximal stomach & proposed the terms short esophagus be abandoned and this condition be simply called "lower esophagus lined by columnar epithelium. Since then columnar lining of the esophagus has become known as Barret's esophagus (Pera et al. 1993)[3]. (Allison& Johnstone 1953)[4] implicated gastro esophageal reflux (GER) as a cause of both the ulcer & development of columnar epithelium in the esophagus. This acquired change is also seen in scleroderma, achalasia & also following anticancer chemotherapy (Mc Kinely& Sherlock, 1984)[5].

Patient with Barrett's epithelium are estimated to at least 30 to 40 times as likely to develop esophageal Cancer as the general population (Cameron et at. 1985)[6].

There are several prognostic factors, that affect survival of patients of adeno carcinoma of the esophagus, (a) Age at presentation; (b) Duration & severity of symptom at presentation; (c) site of tumor; (d) clinical stage of diagnosis(e) Degree of differentiation of the tumor, (f) Vascular lymphatic invasion. Turnbull & Godner (1968)[7] in their study found that the lesion in lower third of esophagus had average survival of 9.6 months with a range of 1 to 41 months & 5yr survival of lower third adenocarcinoma was 2.2% & That of epidermoid carcinoma was 1.5%. Cederqvist et al. (1990)[8] found that lesions in lower third of esophagus has better 5 years survival than upper & middle third & commonest location of

adenocarinoma is in the lower third & GE junction of esophagus.

Mucin secretion is one of the characteristics of the gastrointestinal mucosa and sub mucosal glands. Mucins are glycoproteins found in various tissues. Different portions of the GI tract secrete different types of mucins & this is sometimes reflected in tumors arising from these regions (Reid L and clamp JR, 1978)[9]. Depending on the histochemical reaction, mucins are generally divided into neutral mucins and acid mucins. Acid mucins are further classified broadly into sialated (sialomucins) and sulfated (sulphomucin) types.

Mucin secretion in the esophagus is generally limited to the submucosal glands of the lower esophagus especially,these glands secrete a mixture of neutral and acid mucins (sulphomucin predominantly). Barrett's esophagus is the eponymous designation given to the presence of columnar epithelium (CELO) along the distal esophagus (Bozymski EM et al, 1982)[10].

The specialized columnar epithelium resembles intestinal metaplasia of the stomach. (Jass JR1981)[11], showed that intestinal metaplasiasecreting sulphomucin (typeIIB) is associated with well differentiated adenocarcinoma in CELO. (Jass JR 1979)[12], said, these carcinomas are postulated to progress sequentially from metaplasia to dysplasia and ultimately to adenocarcinoma. Jass claimed that sulphomucin staining might permit identification of patients at risk for developing esophageal adenocarcinoma complicating Barrett's esophagus.

Therefore, while routine methods of staging and grading are helpful, it would be interesting to note, whether mucin histochemistry (which reflects in a way an attempt at differentiation) of such tumors would improve prognostication. Therefore a study designed to examine routine methods of grading and staging & utility of mucin histochemistry regarding prognostication of esophageal adenocarcinoma has been undertaken.

Materials & Methods

All patients of adenocarcinoma of esophagus between January 1980 & December 1995 were considered for inclusion in this study & these patients were operated in Dept. of Surgical discipline, AIIMS, New Delhi in a Single unit.

All patients of adenocarinoma of esophagus, that were located either within the esophagus or gastro esophageal junction with more than 50% of the tumour located within the esophagus, were included in the study. Patients were followed for at least 2 years or till time of death following surgery, whichever is earlier. The patients, that were inoperable or those who died within 30 days post operative, and the patients who do not have adequate history or follow-up, as well as those, whose paraffin blocks were not available in the Dept. of Pathology AIIMS for mucin histochemical study, were excluded.

Out of initial group of 72 patients, a total 52 patients were shortlisted after careful application of inclusion and exclusion criteria and out of that, 7 patients were excluded as main histochemical staining was technically unsatisfactory. Therefore this study was performed on 45 patients.

As a preoperative evaluation, relevant clinical data of patients were retrieved from case records and different clinical variables were compared with special reference to age, sex, symptoms like (dysphagia, retrosternal pain, regurgitation, hematemesis, malena); duration of symptoms, predisposing factors like (tobacco, alcohol).

Routine investigations like CBC, liver function test, renal function test, Ba Swallow esophagus, upper GI endoscopy & ultrasonographic examination of abdomen were done.

Operative Procedure

All patients underwent total esophagectomy with a gastric pull up (esophago-gastrostomy or colonic transposition).

Post operative follow-up were done for a minimum of two years or till death. The follow-up varied between 1 month and 116 months with a mean of 28.9 months and median of 24 months

and they were included as controls, for comparison with those who did not survive for 24 months. There were a total of 45 patients, of which 21 were cases and 24 were controls.

A detailed pathological evaluation was carried out on all cases. Details of gross examination was available from archival records of the Dept. of Pathology, AIIMS by haemotoxylin and eosin stained sections. Location of the tumor, size of the tumor, differentiation of the tumor, depth of infiltration, lymph mode involvement and accordingly stage of the disease are the pathological characteristics, evaluated during this study.

Mucin histochemistry was performed on 45 patients Histochemical identifications of Neutral & Acid Mucins (Sulpho & Sialomucins) were made on paraffin sections, using the AB-PAS & HID-AB reaction.

Statistical analysis

For statistical analysis STATA statistical package (Stata Corporation Texas, USA) and EPIIINFO (WHO) were used.

Measurement of variables were done:

a) the exposure variable depicts the result of mucin staining characteristics of paraffin fixed tissue and those patients, in whom the tumor had one or more of the three types of mucins (sulphomucin, sialomucin, or neutral mucin), were called exposed.

b) The outcome variable tells that, the death due to cancer following esophagectomy, was considered outcome of interest. Patients dying of other causes and those lost to follow up, were censored. The outcome was assessed by reviewing the follow-up records of the patients for the last fifteen years.

Statistical analysis was done.

The Exposure Odds Ratio (OR) was calculated for each type of mucin (viz. Sialomucin, Sulphomucin, neutral mucin), e.g. for sialomucin (SI) : OR (SI)= odds of sialomucin positivity in the cases / odds of sialomucin positivity in the controls.

		Cases	Controls
Sialomucin	Yes	a	b
	No	c	d

OR (SI) = $\frac{ad}{bc}$; similarly OR for other mucins were calculated. The point estimate and 95% confidence interval of Odds Ratio was calculated using STATA Statistical package (Texas, USA).

(ii) Appropriate statistical methods (multivariate analysis) was utilized to correlate various clinical & pathological features with mucin histochemical characteristics. Its association with prognosis was also studied.

Results

There were total of 45 patients of which 21 were cases and 24 were controls.

Patients who survived for a period of at least 24 months were included as controls, for comparison with those, who did not survive for 24 months.

The distribution of age, male & female ratio of the patients with the above two groups were well matched; for cases, the age ranged between 32-68 and the sex ratio was 16 males and 5 females, for controls this was 30 – 70 and sex ratio 20 males and 4 females. The age dependency and sex ratio was not statistically significant.

Table – 1 Compares the grade of cases and controls.

Histological Grade	Cases (n = 21)	Controls (n=24)	Total (n-45)
Well differentiated	11	12	23
Mod Differentiated	2	6	8
Poorly differentiated	8	6	14

MH Chi square = 2.14; P=0.34; statistically insignificant

Table – 2 Depicts Association of stage of tumor with case control status.

Stage	Cases (n = 21)	Controls (n=24)	Total (n-45)
I	1	1	2
II	4	7	11
III	16	16	32

MH Chi square = 2.81; P =0.42, Statistically insignificant

Table: 3 Represents mucin and histological grade in cases and controls

Histological grade	Type of mucin	Cases (n = 21)		Controls (n = 24)		OR	CI	P
		Pos	Neg	Post	Neg			
WD	Neutral	8	5	3	7	3.73	0.49-31.93	0.14 (NS)
	Sialo	3	8	3	7	0.53	0.06-4.05	0.66 (NS)
	Sulpho	4	7	2	10	2.86	0.38-26.42	0.370 (NS)
MD	Neutral	1	1	5	5	5.0	0.01-31.93	0.377 (NS)
	Sialo	Nil	2	4	4	0.0		-
	Sulpho	1	Nil	6	6	0.0		
PD	Neutral	4	4	6	3	1.0	0.08-13.0	1.00 (NS)
	Sialo	3	5	2	4	1.20	0.08-21.0	1.00 (NS)
	Sulpho	5	3	1	5	8.33	0.45-47.11	0.137 (NS)

NS- Not significant

Table: 4 Represents Presence or absence of overall mucins in cases & control

	Cases (n = 21)		Controls (n = 24)				
Type	**Present**	**Absent**	**Present**	**Absent**	**OR**	**CI**	**P**
Any Type	21	0	21	3	-	-	-
Neutral	13	8	9	15	2.71	0.70 – 10.78	0.106(NS)
Acid	19	2	18	6	3.17	0.56 – 17.7	0.26 (NS)
Sialo	6	15	9	15	0.67	0.15 – 2.76	0.53 (NS)
Sulpho	10	11	3	21	6.36	1.23 – 41.64	0.01 (S)

NS – Not significant, S - Significant

Table 5 Depicts Presence or absence of intra cellular mucin in cases and controls

	Cases (n = 21)		Controls (n = 24)				
Type	**Present**	**Absent**	**Present**	**Absent**	**OR**	**CI**	**P**
Any Type	13	8	12	12	1.63	0.49 - 5.34	0.5 (NS)
Neutral	11	10	7	17	2.67	0.67 – 10.95	0.116(NS)
Acid	8	13	9	15	1.03	0.31 – 3.43	1.0 (NS)
Sialo	5	16	7	17	0.76	0.16 – 3.48	0.688 (NS)
Sulpho	5	16	4	20	1.56	0.28 – 9.19	0.55(NS)

NS – Not significant,

Table 6 Presence or absence of extra cellular mucin in cases and controls

	Cases (n = 21)		Controls (n = 24)				
Type	**Present**	**Absent**	**Present**	**Absent**	**OR**	**CI**	**P**
Any Type	18	3	18	6	2.0	0.43 - 9.26	0.46(NS)
Neutral	16	5	13	11	2.71	0.64 – 12.39	0.127(NS)
Acid	16	5	16	8	1.60	0-43 – 5.96	0.52(NS)
Sialo	10	11	13	11	0.70	0.20 – 2.90	0.664(NS)
Sulpho	11	10	4	20	5.50	2.18 – 28.84	0.012(S)

N – Not Significant; S - Significant

Table: 7 a Represents mucin and histochemistry and Stage I in cases & Control

Location	Type of mucin	Cases (n = 1)		Controls (n = 1)	
		Pos.	Neg.	Post	Nes
Any where	Neutral	Nil	1	Nil	1
	Sialo	Nil	1	1	Nil
	Sulpho	1	Nil	Nil	1
Intra Cell	Neutral	Nil	1	Nil	1
	Sialo	Nil	1	1	Nil
	Sulpho	1	Nil	1	Nil
Extra cell	Neutral	Nil	1	Nil	1
	Sialo	Nil	1	1	Nil
	Sulpho	Nil	Nil	Nil	Nil

Table:7b. Represents mucin and histochemistry and Stage II in cases & Control

Location	Type of mucin	Cases (n = 4)		Controls (n = 7)	
		Pos.	Neg.	Post	Neg.
Any where	Neutral	3	1	1	6
	Sialo	1	3	6	1
	Sulpho	1	3	Nil	7
Intra Cell	Neutral	3	1	1	6
	Sialo	2	2	3	4
	Sulpho	Nil	4	1	6
Extra cell	Neutral	2	2	4	3
	Sialo	1	3	7	Nil
	Sulpho	1	3	1	6

Table 7c (s) represents mucin histochemistry and Stage III in cases and control

Location of mucin	Type of mucin	Cases (n = 16)		Controls (n = 16)		OR	CI	P
		Pos.	Neg.	Pos.	Neg.			
Any where	Any type	12	4	16	Nil	0.0	-	-
	Neutral	10	6	8	8	1.67	0.33-8.57	0.48(NS)
	Acid	15	1	9	7	5.0	08.3-30.28	0.10(NS)
	Sialo	5	11	2	14	3.18	0.40-38.12	0.394(NS)
	Sulpho	8	8	3	13	4.33	0.72-31.56	0.067(NS)
Intra Cell	Any type	8	8	9	7	0.98	0.24 - 3.96	1.00 (NS)
	Neutral	9	7	6	10	1.67	0.33 - 8.57	0.48 (NS)
	Acid	4	12	6	10	0.83	0.19 – 3.72	1.00 (NS)
	Sialo	3	13	5	11	0.51	0.07 – 3.39	0.68 (NS)
	Sulpho	4	12	2	14	2.33	0.27–29.34	0.65 (NS)
Extra cell	Any type	15	1	9	7	10.67	1.1 – 1.03	0.03 (S)
	Neutral	14	2	9	7	5.44	1.75 – 50.08	0.053 (NS)
	Acid	14	2	8	8	5.3	1.07 – 26.0	0.06 (NS)
	Sialo	9	7	5	11	2.83	0.54 – 15.45	0.16 (NS)
	Sulpho	10	6	3	13	7.22	1.17-52.78	0.13 (NS)

For the purpose of analysis tumor were classified into three grades. There is no difference in survival in respect to histological grade.

According to chinicopathological characteristics, age & sex distribution, predisposing factors like tobacco and alcohol, symptom duration, size of the tumor, location of the tumor, histological grading, stage of the tumor; there is no difference in the survival (table 1,2& 3).

To Evaluate the mucin histochemical status, the presence of individual types of mucin was noted in three locations, intracellular, extra cellular and overall and survival analysis (outcome variable being death / survival at 24 months) was done with respect to different clinicopatholigical variables and the mucin histochemical findings and also presence or absence of mucin in adenocarcinoma of the esophagus.

Statistical analysis types of revealed that, extra cellular mucin are more frequently found than intracellular mucin (table 4, 5, 6).

Data reveals that the presence of extracellular mucin specially sulphomucin is associated a poor outcome (death within 24 months), OR of 5.50 (P=0.012) i.e. statistically significant (table 6).

Mucin histochemical finding were correlated with outcome variable in different stages of tumor. A relatively detailed analysis was possible in the 32 patients with stage III disease. It was observed that the presence of any type of extra cellular mucin (OR= 10.67, P=0.03) is associated with a poor outcome at 24 months. (Table 7,a,b,c).

Discussion: The study was conducted on 45 patients of adenocarcinoma of the esophagus and gastroesophageal junction operated by a single surgical limit of AIIMS, New Delhi. These cases were more or less selected, in respect to location of tumor and availability of adequate paraffin

blocks and follow up for at least 24 months or death.

Depending on the outcome at 24 months (death or survival) the patients were divided into cases (21) & controls (24). Prognostic variables and the role of mucin histochemistry in the prognosis of esophageal adenocarcinomas were studied. The majority, of these 45 patients were over 40 years with a mean age of 52.43 years. The median age reported by (Fein et al 1985)[13]was 60 years; (Rothwell et al 1997[14])was 69 years, therefore in the present series, median age is a decade earlier, than those reported from West. The sex ratio (M: F): 4:1 is in between that of Rothwell et al (1997)[14]7: 3 and Fein et al (1985)[13] 7: 1. Statistical analysis did not reveal any difference in survival amongst cases and controls with reference to age group and sex. Launois et al (1983)[15] reported a five year survival of 2.5% for patients below 60 years and 3% for those above 50 years.

Four major symptoms were evaluated in this study; dysphagia, regurgitation, retrosternal pain and GI bleeding, these symptoms were indicative of an esophageal lesion, but in no way related to nature or location of the tumor (Sugimachi et al 1987)[16].

The commonest location of adenocarcinoma of the esophagus is considered to be the lower third and GE junction (Cederqvist et al 1980). In this study, all the 45 tumors were located in the lower 1/3rd and GEjunction. The mean survival of lower third tumors was 32 months, whereas those of GE junction and lower 1/3rd was 23 months. This finding is at variance with that of Fein et al (1985)[13]who found the adenocarcinoma of the lower esophagus were that of the adenocarcinomas of the GE junction.

In this study, no difference was found amongst the three grades of differentiation and survival at 24 months (Table 1). This observation in agreement with studies of Skinner et al 1986[18], Sugimachi et al (1988)[17], who could not find any difference in survival with histological grading.

In this present study, the patients were almost identically distributed over different groups, with respect to stage of disease, staging which includes depth of infiltration by tumor and lymph node metastasis (Table 2). Hence, in this selected group of patients, no correlation could be identified between the parameters and outcome at 24 months.

It was observed that neutral and acid mucin were found in combination in most patients. Thus almost 50% (22) tumors had neutral mucins and about 80% (37) had acid mucins (Table 4). Acid mucins, especially sulphomucins, have been described in adenocarcinomas of the GE junctionin Shah & Shri Khande, (1989)[19]. In this study, both sialomucin and sulphomucin were found to an almost identical extent. It was also found, that extracellular mucin predominated over intracellular mucin. No such observation has been reported in contemporary literature.

It is interesting to note that mucin and the presence of acid mucins are associated a poor prognosis. Of the acid mucin, sulphomucin, especially extracellularly are market for poor outcome(table 4,5,6) for presence of intra / extra cellular sulphomucin OR=6.36, P=0.01 (Table 4); For extracellular only OR=5.50, P= 0.012) (table 6).

The importance of mucin histochemistry was further brought out while evaluating patients with stage III disease. Of these, the maximum association was found with sulphomucin especially when found extracellularly (OR=10.67, P=0.03) (table 7c).

Thus the importance of mucin histochemistry as an additional prognostic marker, in adenocarcinoma of the esophagus is well exemplified by this study. In the stomach as well as esophagus, precancerous lesions such as intestinal metaplasia & Barett's esophagus, respectively have been extensively studied. In the stomach, type III intestinal metaplasia with a predominance of sulphomucins is known to be strongly associated with gastric carcinoma.

It is also interesting, in Barett's esophagus, the presence of sulphated mucin has been postulated as a risk of developing esophageal

adenocarcinoma (Jass 1981)[20]. Barret's esophagus was identified in 3 controls only (6.67%). In the literature, the Barret's esophagus was found in upto 86% of patients with distal esophageal carcinoma (Haggitt, 1978)[21].

Extracellular acid mucins (especially sulphomucin) appear to be an important prognostic marker inadenocarcinoma of esophagus as well as adenocarcinoma of stomach and its precancerous lesion, the adenocarcinoma of the esophagus & stomach may have some mucin histochemical similarities and importance.

It is apparent that mucin histochemistry is an important prognostic marker, which needs to be evaluated in a large number of adenocarcinoma of the esophagus.

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