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Significance of Alpha-Methylacyl Co-A Racemase Expression in Gastrointestinal Adenocarcinoma

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Abstract: **Adenomas are more common than adenocarcinoma and only a few out-come malignant. Therefore the use of molecular bio-markers may further aid in determining risk of development of carcinoma in these premalignant lesions. Alpha-methylacyl-CoA racemase is a mitochondrial and peroxisome enzyme involved in beta oxidation of dietary branched fatty acid and their derivatives. A range of neoplastic tissue expresses AMACR.** ***Design:*** **This study was conducted in the department of Pathology Pt. BD. Sharma, University of Health Science, (Rohtak), on fifty cases of GIT adenocarcinoma biopsies/resected specimens and ten cases of adjacent normal mucosa of GI adenocarcinoma specimen which acted as control. Sections from each case were subjected to H&E and immuno-histochemical staining for AMACR expression and analyzed using SPSS.** ***Results:*** **The mean age of participants was 50.36+-16.84. The difference in anatomical location and Colon adenocarcinoma according to laterality of tumor was found to be statistically significant. However, the difference in AMACR expression according to location of tumor, Difference in grades of AMACR expression in various grades of GI adenocarcinoma and difference in AMACR expression according to site and grade of tumor was not statistically significant.** ***Conclusion:*** **AMACR expression appears to be useful marker in the multistep process of carcinogenesis in colorectal carcinoma. However, diffuse varieties including signet ring cell type fail to express this marker. So, AMACR expression could be a indicator of GI adenocarcinomas; however its role as a prognostic marker.**

Keywords: **AMACR, GIT, Adenocarcinoma, Alpha-methylacyl-CoA racemase, Adenomas, Cancer.**

1. INTRODUCTION

Yearly, cancer accounts 12% of the total deaths globally, and in industrialized countries it upto 25% of people die of cancer yearly. The cancer of GIT is responsible for approximate 3 million new cases (stomach, liver, colon and pancreas cancer) and 2 million deaths yearly. Cancer of stomach is the most frequent GIT cancer, irrespective of gender or region specific variation. The primary epithelial tumor of the stomach is the adenocarcinoma, and develops from the stomach mucosa, usually maintaining glandular differentiation.[1] Gastric cancer is the second leading cause of cancer-related death and fourth most common cancer globally. There are several pathways that are involved in gastric carcinogenesis. These are the mammalian target of rapamycin (mTOR) pathway, the Ras/Raf/Kinase/ERK pathway and nuclear factor (NF)-kB pathway. The mTOR pathway is known to regulate protein synthesis, cell-cycle progression, metabolism and angiogenesis. It is regulated via sequential activation of multiple molecules, including alpha-methylacyl-CoA racemase (AMACR).[2]

Colorectal cancer (CRC) is the third most common cancer in men (663,000 cases 10% of total cancers) and the second in women (570.000 cases, 9.4% of the total cases).[3,4] Colon cancer has numerous environmental and demographic risk factors.[5] Comparatively good prognostic factors are stated to be female sex, involvement of left colon, tumor restricted till

Submucosa carcinoma with pushing margins and inflammatory reactions at the tumor and normal tissue interface while through bowel wall invasion, peri-neural or vascular infiltration, presence of obstruction, perforation, tumor budding and peri-colonic tumor deposits are indicators of poor outcome.[6]

Adenomas are more common than adenocarcinoma and only a few outcome malignant. Therefore the use of molecular bio-markers may further aid in determining risk of development of carcinoma in these premalignant lesions.[7] Alpha-methylacyl-CoA racemase is a mitochondrial and peroxisome enzyme involved in beta oxidation of dietary branched fatty acid and their derivatives. It has been demonstrated to be over-expressed in number of tumor especially those linked to high fat diets. A range of neoplastic tissue expresses AMACR, which include colorectal, prostate, ovaries, breast, urinary bladder, lung and kidney. AMCAR is also over-expressed in precursor lesions.[8] The frequent over-expression in prostate cancer has first pointed a role of AMACR in cancer biology, and AMCAR expression analysis has soon become a routine tool in prostate cancer diagnosis. Subsequent studies have revealed that AMCAR is over expressed many other tumor type. The potential utility of AMCAR analysis in the diagnosis of dysplasia has been widely studied, especially in GIT pathology. Various studies have analyzed AMACR expression in adenocarcinoma of the colon, where it is thought to be associated with tumor differentiated and localization.

2. METHODS & MATERIALS

Present study was conducted in the department of Pathology Pt. BD. Sharma, University of Health Science, Rohtak, included of fifty cases of GIT adenocarcinoma biopsies/resected specimens and ten cases of adjacent normal mucosa of gastrointestinal adenocarcinoma specimen which acted as control. Clinical details were recorded. H&E and immuno-histochemical (AMACR) stains were performed on 4-5 um histological sections and examined. All carcinoma were graded according to WHO grading system for gastrointestinal carcinomas.

Exclusion criteria: Cases with poorly preserved morphological details, inadequate biopsy, inadequate cellularity biopsies with marked inflammatory changes and malignancies other than the adenocarcinomas. **Immunoquantitation:** Each slide was evaluated at 40X magnification in order to find areas with maximum positive cells. Then these cells were further examined at 200X magnification and the percentage of positive cells. AMACR expression in tumor was divided in for graded:

1) 0 negative (0cells positive)
2) 2) 1+ 1-10% cell positive
3) 2+ 11-50% cell positive
4) 4) 3+> 50% cells positive

Statistical Analysis: The results were tabulated and analyzed using SPSS. Data were expressed as mean variables, numbers and percentage. The correlation between tumor grades and immuno-histochemical expression was analyzed using Spearman's correlation test with occupying-value.

3. RESULTS

This study was conducted on a total of 50 cases of GIT adenocarcinoma comprising of 8 excised GI segment and 42 trucut biopsies. 10 cases with normal adjacent mucosa which acted as control were also included in the study. AMACR expression was evaluated in each case and correlated with site type and differentiation of the gastrointestinal adenocarcinoma and analyzed statistically.

TABLE 1: DISTRIBUTION OF CASES ACCORDING TO AGE OF PATIENTS (N=50)

Age in years	No. of CASES	Percentage (%)
10-19	2	4
20-29	4	8
30-39	1	2
40-49	16	32

50-59	11	22
60-69	10	20
70-79	4	8
80-89	2	4
Total	50	100
Mean ±SD	**50.36±16.84**	

Table 1: The patients were tabulated for the study in the age group of 10-89 years with the class interval of 10 years. The youngest patient was 18 years old and oldest patient was 86 years old and observed the maximum numbers of cases were in the age group of 40-69 years forming 74.0% of the total cases. The mean age group was 50.36+-16.84**.**

The male to female patient ratio was 1:1. According to location of tumor, maximum number of cases were reported in colon forming 40 (80%) and next, stomach 7 (14%). Esophagus and small intestinal adenocarcinoma comprised 2 and 1 case respectively. According to the location of tumor in colon **(n=40),** maximum number of cases 16 (40%) were reported in rectum followed by sigmoid colon with 15 (37.5%) of cases, none of the tumor was found in transverse colon. Ascending colon consisted 6 (15%) cases and descending colon consisted of 3 (7.5%) cases only.

The mostly GI adenocarcinoma clinical feature was bleeding per-rectum was present in 21 (42%) cases followed by constipation in 15 (30%). Dysphasia in 4 (8%), vomiting and nausea in 6 (12%) were presenting complaints, while other chief complaints comprised of pain abdomen, and blood in stool consisting of 3 (6%) and 1 (2%) cases respectively. Most of tumor of Colonic adenocarcinomas (34/40) was reported in left side of body i.e. in colon and rectum while only 6 cases had tumor on right side. This difference in anatomical location was statistically significant (p value=0.000).

GI adenocarcinoma according to the differentiation of tumor, maximum number of cases 41 (82%) were of moderately differentiated adenocarcinoma whereas 9 (18%) were poorly differentiated adenocarcinoma/mucinous adenocarcinoma.

TABLE 2: CORRELATION OF AMACR IMMUNOSTAINING WITH THE TYPE OF TISSUE STAINED (n=60)

Nature of Tissue	AMACR +VE	AMACR -VE	Total
Normal GI Epithelium	0	10	10
GI Adenocarcinoma	30	20	50
Total	30	30	60

Table 2: illustrates, none of the normal epithelium showed positive expression for AMACR. 30 out of 50 cases of gastrointestinal adenocarcinoma was positive expression for AMACR. Further on calculating the sensitivity came out to be 60% and specificity 100% with positive predictive value of 100% and negative predictive value of 33.3% thus signifying its up regulation in neoplasia and further stressing that AMACR may serve as useful marker for differentiating neoplastic epithelium from non-neoplastic epithelium.

The distribution of AMACR positivity in GI adenocarcinoma cases according to the location of tumor. Out of 40 cases of colon carcinoma 28 cases were positive for AMACR expression. Only one case of ileal adenocarcinoma included in the study was negative for AMACR expression. Two out of seven gastric adenocarcinoma cases were positive and both were intestinal type while both the cases of esophagus were negative for AMACR expression. Difference in expression was statistically significant (0.029) at various GI sites.

TABLE 3: AMACR EXPRESSION IN VARIOUS HISTOLOGICAL SUBTYPES OF GASTROINTESTINAL ADENOCARCINOMA

Site		**AMACR Expression**		**Total**
		POSITIVE	**NEGATIVE**	
Esophagus	**Adenocarcinoma**	**0**	**2**	**2**
Gastric	**Intestinal**	**2**	**2**	**2**
	Diffuse	**0**	**3**	**5**
Small	**Adenocarcinoma**	**0**	**1**	**1**

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Intestine				
Colon	**Adenocarcinomanos**	**28**	**8**	**36**
	Mucinous Adenocarcinoma	**0**	**4**	**4**
Total		**30**	**20**	**50**

Table 3: illustrate AMACR expression seen according to various histological grades of tumor types. Negative AMACR expression was seen in the tumor of esophagus, diffuse infiltrating adenocarcinoma of stomach, small intestine and mucinous adenocarcinoma of colon. 2/4 intestinal type gastric adenocarcinomas revealed positive AMACR expression. In colon 28/40 cases were positive for AMACR expression, including 3 cases of poorly differentiated type were positive.

AMACR expression of colon at different sites, maximum number reported in rectum and sigmoid colon, 16 and 15 respectively out of which 75% and 73% cases revealed positive AMACR expression in respectively. In ascending-colon only 2/6 (33%) revealed positive AMACR expression while in descending colon all 3 (100%) were positive for AMACR expression. However, the difference in AMACR expression according to location of tumor was not statistically significant (p value<0.145). Colon adenocarcinoma according to laterality of tumor were seen in 76% and of the left side tumor were AMACR positive but only 33.3% were positive on right side. This association was found to be statistically significant (p Value=0.026).

GI adenocarcinoma with AMACR immuno-staining resulted that the maximum number of cases belonged to moderately differentiated adenocarcinoma (41/50). 27/41 revealed positive AMACR expression with 12, 8, 7 cases of 1+, 2+, 3+ positivity respectively while in poorly differentiated tumor which consisted 4 mucinous and 5 poorly differentiated adenocarcinoma, only 3 out of 5 poorly differentiated adenocarcinoma revealed positive expression with 2 and 1 cases revealing 2+ and 3+ positive AMACR expression respectively. Difference in grades of AMACR expression in various grades of GI adenocarcinoma was not statistically significant (p value=0.189).

TABLE 4: DISTRIBUTION OF GASTROINTESTINAL ADENOCARCINOMA CASES ACCORDING TO THE AMACR EXPRESSION GRADES IN VARIOUS SITES.

	SITE	**AMACR XPRESSION**				**Total 10**		**P Value**
		1+	**2+**	**3+**	**Negative**			
Normal GI Epithelium		**0**	**0**	**0**	**10**			**0.007**
Adenocarcinoma	**Oesophagus**	**0**	**0**	**0**	**2**	**2**		
	Gastric	**1**	**1**	**0**	**5**	**7**		**0.078**
	Small Intestine	**0**	**0**	**0**	**1**	**1**		
	Ascending colon	**1**	**1**	**0**	**4**	**6**		
	Descending colon	**2**	**1**	**0**	**0**	**3**		
	Sigmoid colon	**6**	**4**	**1**	**4**	**15**		
	Rectum	**2**	**3**	**7**	**4**	**16**		

Table 4: show the grades of AMACR expression in GI adenocarcinoma at various location and in normal gastrointestinal epithelium. Ten cases of normal epithelium did not reveal AMACR expression and in 50 adenocarcinomas cases 30 revealed positive expressions. Cases of esophagus and small intestine did not reveal AMACR expression while in stomach 2/5 cases revealed positive expression of grade 1+ and 2+ and none of the case revealed 3+ expressions. In Ascending and descending colon also 1+ and 2+ expression was seen while in sigmoid and rectum positive expression was seen in 73% and 75% cases with 3+ grades in 8 cases. Statistical analysis revealed statistical significant difference in

AMACR expression. However, difference in AMACR expression according to site and grade of tumor was not statistically significant.

4. DISCUSSION

Gastrointestinal tumors constitute one of the major causes of morbidity and mortality worldwide and include both benign and malignant tumors. All malignant disease and colorectal carcinoma are the commonest malignancy of GIT followed by gastric and esophageal carcinoma.[1,4] Alpha-methylacyl-CoA racemase (AMACR) is a mitochondrial and peroxisome enzyme involved in beta-oxidation of dietary branched chain fatty acids and their derivatives.[5] It has been demonstrated to be over-expressed in number of tumors especially those linked to high fat diets. A range of neoplastic tissues expressing AMACR includes colorectum, prostate, ovaries, breast, urinary bladder, lung and kidney. AMACR is also over-expressed in precursor lesions.[7,8]

In gastrointestinal tract tumours, expression of AMACR has been shown in 25% of gastric adenocarcinomas, 75% of colonic adenomas and in most of the moderately and well-differentiated colonic carcinomas, but not in normal gastric, small intestinal and colonic epithelium. These studies suggest that AMACR can be a biomarker for epithelial malignancies of the gastrointestinal tract. The aim of this study was to evaluate the expression of AMACR in the gastrointestinal adenocarcinomas and to determine its significance.[6,9]

Age and Sex Distribution: The results of present study are similar to result of previous studies which reported that incidence of GI cancer increases progressively from 40 years of age, rising sharply after the age of 50. More than 90% of colon cancer occurs in people aged ≥50 years. However, literature also stresses that colorectal cancer has increasingly being seen in younger patients. We too reported 7 patients were belongs to <40 years of age. In our study, male to female ratio was 1:1. This is in concordance with the study done by Zong Ming E and Chen et al who also found that men and women were affected almost equally.[9,10]

Location and Grade of Tumor: Maximum number of cases was reported in colon forming 80% of total cases. Next frequency was stomach 14% cases. Esophagus and small intestinal adenocarcinomas comprised 4% and 2% case respectively. This is in accordance with result of previous study done by Zhong et al.[11] They also observed that small intestine though constitutes 75% of length and almost 90% of mucosal surface of gastrointestinal tract is a rare site for malignancy. Adenocarcinoma of small intestine is only 1/50th as common as colorectal carcinoma.[10] Most of the cases of colorectal carcinoma were located in rectum and sigmoid colon (31/40) whereas 6 cases were reported in ascending colon and 3 in descending colon. None of the case was seen in transverse colon. This difference in location is best explained by advances in understanding of molecular causes and availability of colon cancer screening.[10] In this study most of the cases (41/50) were found to be moderately differentiated whereas 9 were poorly differentiated including 4 cases of mucinous type adenocarcinoma. This is in accordance with study done by Yujiro et al who observed high percentage of moderate grade tumour (23/40) in comparison with poorly differentiated (11/40) and well differentiated tumour (6/40).[12]

AMACR: Present study in neoplastic epithelium including 30/50 cases of GI adenocarcinoma were signifying its positive expression as useful indicator of malignancy. This is in concordance with the result of previous studies (Table 8) in which it has been observed to be useful marker for cancer as it was not expressed in normal gastric, small intestinal or colonic epithelium or expression was observed in very small percentage of cases (<5%) which may reflect nonspecific protein binding.[5,13]

TABLE 5: COMPARISON OF AMACR EXPRESSION SEEN IN GASTROINTESTINAL ADENOCARCINOMA IN VARIOUS STUDIES WITH PRESENT STUDY

STUDY	Year	+ ve AMACR EXPRESSION	SITE	P value
Jiang et al[11]	2003	75%	Colon	NM*
Nassar et al[13]	2005	44.8%	Colon	NM*
Chen et al[10]	2005	62%	Colon & small intestine	<0.0001
Dorer et al[14]	2006	71%	Colon	<0.0001
Lee et al[9]	2006	51.5%	Gastric	<0.05

Lin et al[15]	2007	75%	Colon	<0.001
Shi X et al[16]	2007	80%	Colorectal	NM*
Marx et al[17]	2008	81.5%	Colon	<0.0001
Huang et al[18]	2008	52.9%	Gastric	=0.070
Yujiro et al[12]	2012	69.7%	Gastric	=0.001
Present Study	2014	60%	GI Tract	<0.029

**NM –Not Mentioned*

Correlation of AMACR Expression with Site and Type of Tumor: Out of 50 cases, 40 were seen in colon and 10 were distributed in other site & including esophagus, stomach and small intestine. Cases of oesophageal 2 and small intestinal 1 adenocarcinoma did not reveal AMACR expression. This is in accordance with study conducted by Wong et al who observed AMACR expression in only 1 out of 24 cases of small intestinal adenocarcinoma.[19] Zong Ming et al found positive AMACR expression only in 3 out of 59 cases of small intestinal adenocarcinoma while in colorectal cancer 62% cases revealed positive expression. They concluded that small intestinal adenocarcinomas are morphologically indistinguishable from colorectal adenocarcinoma but the etio-pathogenetic mechanism involved is different and so statistical significant difference in AMACR expression is seen.[10] In our study due to one case of small intestinal adenocarcinoma, so that statistical correlation could not be done.

Dorer et al. however, noted positive AMACR expression in Barrett's esophagus with dysplasia and stated that AMACR may be useful marker to detect neoplastic epithelium in esophagus. In our study only 2 cases of oesophageal adenocarcinoma were there so further evaluation is needed in more patients.[14] There was 7 cases of gastric adenocarcinoma in our study out of which 4 were of intestinal type. 2/4 intestinal type adenocarcinoma cases revealed positive expression whereas AMACR expression was negative in all 3 cases of diffuse infiltrating type of adenocarcinoma cases. Our findings are in concordance with study which suggested that AMACR may play a role in the intermediate stage of gastric carcinogenesis and found it to be uniformly negative in groups negative for dysplasia and indefinite for dysplasia and positive in high grade dysplasia and invasive intestinal type adenocarcinoma (76% and 52.9% respectively).[15] Yujiro et al also observed AMACR expression correlation with mucin phenotype in gastric adenocarcinoma. They observed significantly higher expression in intestinal type than in gastric type carcinoma .[12]

No significant difference in AMACR expression was seen in various sites of colon but when compared according to laterality of tumor significant difference in AMACR expression was observed. Two of the 6 adenocarcinoma cases on right side of colon revealed positive AMACR expression and 26 of 34 located on left side revealed positive AMACR expression (33.3% and 76.4% respectively). Our findings are in concordance with study done by Andreas et al who also observed AMACR expression in colorectal cancer associated with left sided tumour localization which may be related to difference in metabolism/exposure to fatty acid occurring along the colon.[17]

TABLE 6: CORRELATION OF AMACR EXPRESSION WITH GRADE OF TUMOR

STUDY	Correlation	P value
Chen et al[9]	Present	<0.0001
Shi X et al[16]	Present	NM*
Marx et al[17]	Present	<0.0001
Lin et al[15]	Present	<0.001
Nozawa et al[12]	Present	=0.001
Present study	Absent	0.189

**NM -Not Mentioned*

Anne Lin et al in their study correlated AMACR expression with tumour pathologic features and concluded that lack of staining or low intensity staining correlated significantly with mucinous histology, poor tumor differentiation and with worse disease specific survival.[15] Shi X et al.[16] Zong Ming et al too reported that AMACR appeared less frequently in mucinous or poorly differentiated colorectal adenocarcinoma when compared with non mucinous or better differentiated counterparts, suggesting an association with microsatellite instability (MSI) status.[10]

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5. CONCLUSION

AMACR expression appears to be useful marker of deviation from normal epithelium in the multistep process of carcinogenesis in colorectal carcinoma depicted morphologically in normal-adenoma-carcinoma sequence. Its expression in other gastrointestinal carcinomas in cases with intestinal type of morphology is also valuable. However, diffuse varieties including signet ring cell type fail to express this marker. So, AMACR expression could be a indicator of intestinal type of gastrointestinal adenocarcinomas; however its role as a prognostic marker needs to be evaluated further.

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