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Original Article

Pathology Section

Expression of Alpha Methyl Acyl Co-enzyme Racemase in Gastric Carcinomas

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ABSTRACT

Introduction: Alpha-Methyl Acyl-Co-enzyme Racemase (AMACR, EC 5.1.99.4, also known as P504S) is a mitochondrial and peroxisomal enzyme involved in branch fatty acids oxidation. High dietary intake of branched fatty acids may result in overproduction of AMACR, which is associated with the development of many cancers including prostate, kidney, breast, ovary, liver and gastrointestinal cancers. Several reports have also shown an association between consumption of fat and increased risk of gastric cancer, especially intestinal type gastric carcinomas.

Aim: To determine and compare the expression of AMACR in clinical types and various histological grades of gastric carcinomas.

Materials and Methods: This was a cross-sectional study conducted from November 2016 to May 2018 at Osmania Medical College/General Hospital, Hyderabad, Telangana, India. The tissue cores of the included biopsied samples of 50 gastric carcinomas, with regions of interest were removed to prepare a tissue microarray and Immunohistochemical (IHC) staining for AMACR was performed. The stained slides were graded based on the intensity of staining and results were evaluated using Chi-square test.

Results: Of the 50 gastric carcinoma (32 males and 18 females; age range: 22-80 years) cases studied 26 were intestinal type and 24 were diffuse type. According to cancer grade, 17 were well differentiated, 09 were moderately differentiated and 24 were poorly differentiated. Abnormal AMACR staining was seen in 73.07% (19) cases of well and moderately differentiated adenocarcinoma and 33.33% (8) cases of poorly differentiated adenocarcinoma. AMACR staining was found to be statistically significantly associated with the differentiation grading of the tumour (p-value 0.016). Abnormal staining for AMACR was seen more in well differentiated compared to moderately and poorly differentiated carcinomas. IHC expression of AMACR showed a statistically significant correlation with Lauren's type of gastric cancer (p-value 0.005).

Conclusion: AMACR is a racemase present in the cytoplasm; cytoplasmic staining is observed in gastric carcinoma and also with histological grade. Abnormal staining for AMACAR was seen more in well differentiated compared to moderately and poorly differentiated carcinomas. The expression of AMACR was significantly higher in intestinal type gastric carcinoma. Hence, the role of AMACR as a target for treating gastric cancer seems to be promising. Further studies are required to establish the role of AMACR as a diagnostic, therapeutic and prognostic tool in gastric malignancies.

Keywords: Diffuse type, Gastric cancer, Intestinal type

INTRODUCTION

Gastric cancer is the fifth most common malignancy in the world, after cancers of the lung, breast, colo-rectum and prostate. Stomach cancer is the third leading cause of cancer death in both gender worldwide (723,000 deaths, 8.8% of the total). The highest estimated mortality rates are in eastern Asia (14.0 per 1,000,00 in men, 9.8 per 1,000,00 in women) and the lowest in northern America (2.8 and 1.5, respectively) [1]. Annual incidence rate of gastric cancer in India is low as compared to the western countries. Incidence of gastric carcinoma is relatively high in southern India. Increase in the incidence is also being reported in north-eastern India [2]. Geographic variability is because of the interaction of host genetic factors and socio-environmental factors. Approximately, 34,000 new cases are reported every year in India which is expected to rise to 50,000 by the year 2020 [3]. Increase in incidence is due to *Helicobacter pylori* infection, diet and lifestyle modifications, tobacco, alcohol and genetic susceptibility. The signs and symptoms are often reported late, when the disease is in advanced stages.

Gastric cancer is mainly classified into two histological subtypes: Intestinal and Diffuse. Intestinal-type gastric cancer is more common in the older age and in high incidence areas. Diffuse-type of gastric cancer is common in the younger population, with an obvious hereditary form [4].

Gastric carcinogenesis is a multistep and multifactorial process. Numerous abnormalities of expression have been reported in molecules modulating growth and cell division such as tyrosine kinase growth factor receptors, p53 and other apoptosis-related genes and genes controlling intercellular adhesion [5,6]. Emerging evidence suggests that there are several interconnected signaling pathways that are involved in gastric carcinogenesis and are being currently investigated. These are the mammalian target of rapamycin (mTOR) pathway, the Ras/Raf/Kinase/ERK (Extracellular Receptor Kinase) pathway and the Nuclear Factor (NF)-κB (NF-kappa B) pathway [7]. 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 AMACR [8].

AMACR, EC 5.1.99.4, also known as P504S is a mitochondrial and peroxisomal enzyme involved in branch fatty acids oxidation [9]. In mammalian cells, the enzyme is responsible for converting (2R)-methylacyl-CoA esters to their (2S)-methylacyl-CoA epimers and known substrates, including co-A esters of pristanic acid (mostly derived from phytanic acid, a 3-methyl branched-chain fatty acid that is abundant in the diet) and bile acids derived from cholesterol. This transformation is required in order to degrade (2R)-methylacyl-CoA esters by β-oxidation, which requires the (2S)-epimer. The enzyme localised in peroxisomes and mitochondria, both of which are known to β-oxidize 2-methylacyl-CoA esters [10,11]. The expression of AMACR has been investigated in many cancers including prostate, kidney, breast, ovary, liver and gastrointestinal cancers as well as some types of precancerous lesions [12-16]. Overexpression of AMACR is seen in normal tissue, such as

hepatocytes, tubular epithelial cells of kidney, bronchial epithelial cells and mucosal epithelial cells of gallbladder [17]. Several reports have shown an association between consumption of fat and increased risk of gastric cancer, especially intestinal-type gastric carcinomas [18-20].

The exact mechanism by which a high fat diet contributes to tumourigenesis in gastric cancer is not clear, but emerging evidence suggests that the Peroxisome Proliferator-Activated Receptor (PPAR)-mediated pathway plays a critical role [21]. PPAR gamma expression in human gastric carcinomas and its effect on proliferation of gastric carcinoma cell lines have been proved [22], while AMACR was not expressed in normal gastric mucosa by real-time Polymerase Chain Reaction (PCR) analysis. Confirming AMACR's role in diagnosis and therapy requires a thorough understanding of the function of AMACR in gastric tumourigenesis. There is a need to explore new markers for early detection of gastric carcinoma on small biopsies which might help to improve the prognosis of the patients. AMACR's role as a potential target for treating gastric cancer seems to be a promising option. Therefore confirming relationship of AMACR expression with tumourigenesis needs to be established.

MATERIALS AND METHODS

A cross-sectional study was carried out, over a period from November 2016 to May 2018 at Department of Pathology, Osmania General Hospital, Hyderabad, a Tertiary Care Centre in Telangana, India after obtaining the consent and Ethics Committee approval for the same (IEC number-1611800147D).

Inclusion criteria: All the specimens of gastric carcinoma which were surgically excised or biopsied and received with adequate tumour tissue for analysis till April 2018, by the Department of Pathology, were included in the study.

Exclusion criteria: Those samples with inadequate tumour tissue for analysis and the ones with history of any prior treatment were excluded from the study.

The data was collected for a total of 50 samples, was analysed in May 2018. Haematoxylin and Eosin-stained sections of these cases were reported according to Lauren's classification [23] as: Intestinal type-26, Diffuse type-24. Representative areas of gastric carcinoma were marked on the slides and the corresponding blocks. Using a hollow needle, tissue cores with regions of interest were removed to prepare a tissue microarray for IHC staining. The six cores of 5 mm each were arranged on each slide. The kits for AMACR IHC staining were obtained from DAKO Company. Staining was done according to manufacturer's protocol. Tissue sections from prostatic cancerous lesions were taken for comparison of AMACR staining expression.

Method of Immunohistochemical (IHC) Staining

Two micro sections, 4-5 µm thick, from each tissue microarray paraffin block were taken on poly-L-lysine coated slides for immunostaining. The fibroblasts and lymphocytes in these samples were taken for comparing AMACR staining in normal cells. Two micro sections of 4 µm thickness were prepared from each of the tissue microarray paraffin blocks and taken on poly-L-lysine coated slides for immunostaining of AMACR. Slides were deparaffinised and antigen epitopes were retrieved using dako buffer. After Trisaminomethane (Tris) wash, slides were incubated with primary monoclonal rabbit anti-human antibody DAKO Clone 13H4, diluted 1:200 for 60 minutes in room temperature and subsequently stained with dako EnVision (K4003) and 3,3′-Diaminobenzidine (DAB) kits for 30 and 5 minutes, respectively. After washing in distilled water and counter staining nuclei with haematoxylin, the slides were ready for the analysis.

Scoring and evaluation: AMACR expression was assessed semi-quantitatively in four (0-3) grades. Expression of AMACR is indicated by a distinctive, coarse intracytoplasmic granularity. To prevent any bias, the prostate cancer tissue and normal lymph nodes were taken for comparison and AMACR scoring.

A scale of 0 to 3 was used to grade the expression [24].

0-no expression

1-up to 50% of cells with detectable staining-weak expression

2-50-75% of cells with moderate staining-intermediate expression

3-more than 75% of cells with intense staining-strong expression.

STATISTICAL ANALYSIS

Correlation between AMACR expression and clinicopathological factors was evaluated using Chi-square test. The p-values <0.05 were considered to be statistically significant.

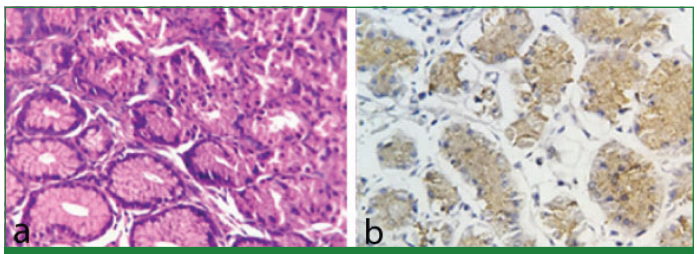
RESULTS

In the present study, 50 cases of gastric carcinoma, 32 males and 18 females in the ratio of 1.7:1, were included. Age of patients ranged from 22 to 80 years. The mean age was 53.6 years and the median was 57 years. Majority of cases were seen in the fifth and sixth decade in females and the seventh decade in males. Majority of patients presented with complaints of indigestion; a few with abdominal pain and dark stools. On endoscopy, an ulcerated lesion was the most common finding. Majority of the cases involved the pyloric antrum region followed by the body [Table/Fig-1].

Demographic and clinical variables		AMACR expression		p-value
		Positive	Negative	
Sex	Males (n=32)	19	13	0.309
	Females (n=18)	8	10	
Location	Pylorus	16	7	0.073
	Body	4	8	
	Antrum	5	2	
	Fundus	2	4	
	Cardia	0	2	
Grade	Well differentiated	13	4	0.016
	Moderately differentiated	6	3	
	Poorly differentiated	8	16	

[Table/Fig-1]: Comparison of AMACR expression in different variables
AMACR: Alpha-methyl acyl-coenzyme racemase; p-values calculated by Chi-square test; p-value<0.05 to be significant; bold p-values denote significance

According to histological grade [Table/Fig-1], 17 well differentiated, 09 moderately differentiated and 24 poorly differentiated cases, the AMACR expressions were found to be associated in statistically significant manner (p-value: 0.016), well differentiated as shown in [Table/Fig-2a,b], moderately differentiated as shown in [Table/Fig-3a,b] and poorly differentiated is shown in [Table/Fig-4a,b].

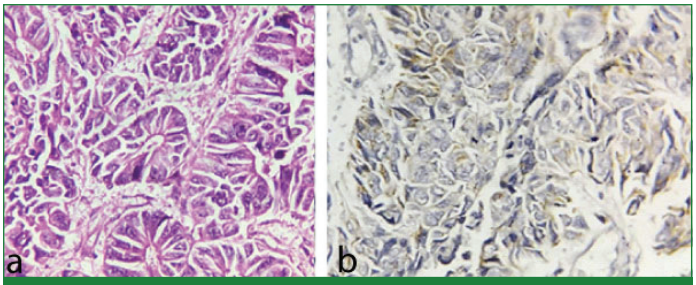


[Table/Fig-2]: a) Well-differentiated adenocarcinoma (well-formed glands with uniform, basally oriented nuclei); H&E- 40X; b) Well differentiated adenocarcinoma (well-formed glands with uniform, basally oriented nuclei); glands showing cytoplasmic granular positivity on AMACR immunostaining- 40X.

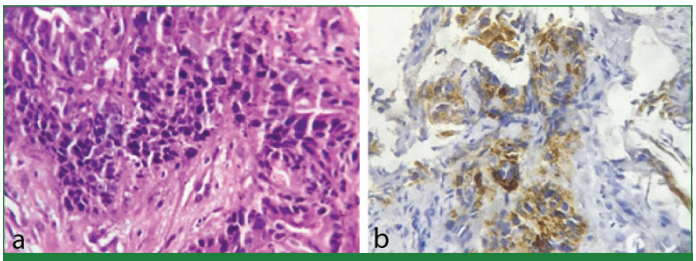
As per Laurens' classification, the cases were grouped as intestinal type-26 cases and diffuse type-24 cases. Distribution of cases in relation to AMACR expression across Laurens'groups has been mentioned in [Table/Fig-5].

Comparison of tumour grading and Lauren's groups with the AMACR expression score has been depicted in [Table/Fig-6].

By analysing the p-value using Chi-square test, the association between Laurens' group and Histological grade with AMACR expression was



[Table/Fig-3]: a) Moderately differentiated adenocarcinoma (glands are simple, complex or slightly irregular; nuclear polarity is lost) H&E- 40X; b) AMACR immunostaining in moderately differentiated adenocarcinoma (glands are simple, complex or slightly irregular; nuclear polarity is lost)- 40X.



[Table/Fig-4]: a) Poorly differentiated adenocarcinoma (<50% of gland formation; majority of tumour consists of sheets of cells without gland formation H& E- 40X; b) AMACR immunostaining in poorly differentiated adenocarcinoma- 40X.

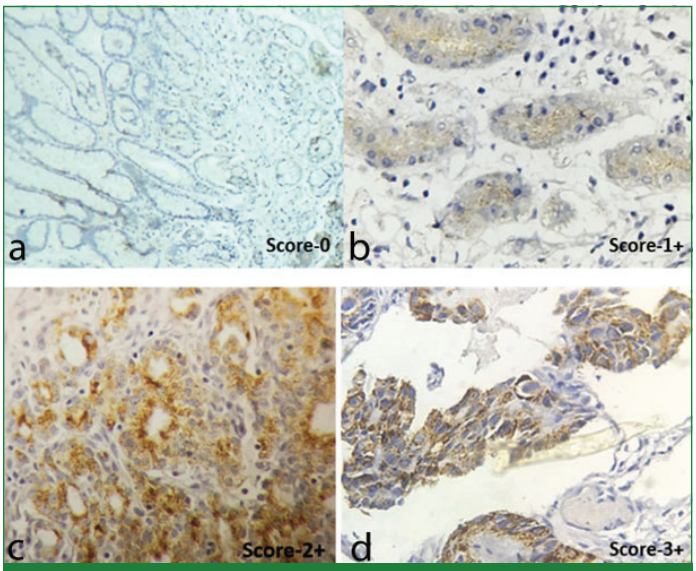
Laurens' classification	AMACR positive	AMACR negative	p-value
Intestinal	19	7	**0.005**
Diffuse	8	16	

[Table/Fig-5]: Comparison of AMACR expression in Laurens Groups.
p-values calculated by Chi-square test; bold p-vales denote significance; AMACR expression positive for n=27; AMACR expression negative for n=23

Histological grading and clinical types		AMACR staining score			
		0	1	2	3
Grade	Well differentiated	4	4	3	6
	Moderately differentiated	3	3	2	1
	Poorly differentiated	16	4	3	1
Laurens'	Intestinal	7	8	4	7
	Diffuse	16	3	4	1

[Table/Fig-6]: Comparison of AMACR expression score with tumour grading and Lauren's groups; AMACR expression positive (score 1-3) for n=27; AMACR expression negative (score 0) for n=23.

found to be statistically significant (p-value <0.05) [Table/Fig-1,5]. The AMACR expression scoring has been shown in [Table/Fig-7].



[Table/Fig-7]: AMACR immunostaining- 40X magnification: a) Score-0: Shows no expression; b) Score 1: Upto 50% of cells shows detectable staining-weak expression; Score: 2: 50% to 75% of cells with moderate staining-intermediate expression; d) Score: 3: >75% of cells with intense staining-strong expression.

DISCUSSION

Incidence of gastric cancer is higher in Southern India as compared to that of Northern part. A mixture of host genetic factors and socio-environmental factors lead to development of gastric cancer. Early detection of the condition and exploration of novel markers will result in better prognosis. A total of 50 cases of gastric adenocarcinomas were analysed, to study the expression pattern of AMACR across various types and grades of cancer. Male to female ratio of the cases was 1.7:1 with 32 males and 18 females. The ages of the patients ranged from 22 to 80 years with the majority of cases seen in sixth and seventh decade. As per [Table/Fig-8], the range of the ages was comparable to the studies done by Mroz A et al., Cho EY et al., Truong CD et al.,and Huang W et al., [24-27]. The age in various studies ranged from 21-93 years. The median age were also comparable in those studies. In the present study, the number of cases below 30 years of age was only three and below 40 years were six.

Comparative analysis with previous studies	Publication year	Age range (years)	Median (years)	M:F	Well, moderately and poorly differentiated AMACR positive	AMACR negative
Cho EY et al., [25]	2007	24-78	59	2.4:1	57.7% of total gastric carcinomas	42.3% of total gastric carcinomas
Truong CD et al., [26]	2008	21-93	65.1	1.7:1	68.8% of total tumour cases	31.2% of total tumour cases
Mroz A et al., [24]	2013	30-85	62.9	2.03:1	57.3% of gastric cancers	42.7% of gastric cancers
Huang W et al., [27]	2008	23-81	45.2	2.35:1	32.1% of total gastric cancers	67.9% of total gastric cancers
Present study	2022	22-80	57	1.7:1	54% of total gastric carcinomas	46% of total gastric carcinomas

[Table/Fig-8]: Expression of AMACR in gastric adenocarcinomas compared with previous studies.
M: Male; F: Female; AMACR: Alpha-methyl acyl-coenzyme racemase [24-27]

When different studies were analysed [24-27], all of them showed male preponderance. In the present study, there was a male preponderance in incidence of gastric carcinoma with a male to female ratio of 1.7:1. Staining patterns of AMACR were evaluated in gastric carcinomas. AMACR expression in cases of adenocarcinoma also showed a male preponderance [Table/Fig-8] [24-27].

The association between the expression of AMACR and the histological type of gastric Adenocarcinoma (Lauren's Classification) was studied and the expression of AMACR was significantly higher in intestinal-type gastric carcinoma.

The expression of AMACR in gastric adenocarcinomas was compared with other studies [Table/Fig-8]. In the present study, 73.07% (19/26) cases of well and moderately differentiated adenocarcinoma and 33.33% (8/24) cases of poorly differentiated adenocarcinoma are positive for AMACR staining. staining. These results were comparable with other studies [24-27].

In the present study, authors used the same monoclonal antibody as Cho EY et al., Mroz A et al., and Truong CD et al., [24-26] which enhances the comparability of results. Similarly, authors did not observe AMACR expression in non neoplastic tissue, which was underlined by other authors both on IHC and molecular grounds. IHC tests were performed simultaneously, and all gastric cancer cases were sectioned and stained in the same conditions.

In the present study, a semi-quantitative immunoreactivity score was used which was similar to that used by Truong CD et al., similar proportions of different AMACR expression intensity groups were observed [26]. Criteria for semi-quantitative AMACR assessment are not established yet, and systematic approach in many comparative studies is mandatory. According to Mroz A et

al., Truong CD et al., and Lee WA, the expression of AMACR was significantly higher in intestinal-type gastric carcinoma [24,26,28]. In the present study, 19/26 and 8/24 of intestinal-type and diffuse-type cancers respectively, displayed AMACR expression. Truong CD et al., however, concentrated only on histologic differentiation of the tumour, whereas Lee WA analysed cases according to the Lauren classification [26,28].

The location of the tumour was not associated with AMACR expression in the present study, neither was it in a study from Mroz A et al., and Huang W et al., AMACR could serve as a biomarker in distinguishing high grade dysplasia from cases with low grade dysplasia [24,27]. Even greater proportion of AMACR positivity in dysplastic gastric epithelium (83.3%) was recorded by Lee WA [28].

It was suggested that AMACR expression could serve as an IHC adjunct in distinguishing neoplastic from reactive lesions in gastric biopsy. In the present study, there were only a few cases having high grade dysplasia adjacent to well differentiated adenocarcinoma, and all of them displayed intensive positivity for AMACR, which corresponds to Huang W et al., and Lee WA observations [27,28].

In adenocarcinomas, AMACR expression is associated with the degree of tumour differentiation, but not with disease stages. This result was similar to that observed in colorectal carcinoma. In the study by Zhou M et al., 20 of 24 (83%) colorectal adenocarcinomas stained positive for AMACR [29]. Among them, 16 were well to moderately differentiated, all of which showed positive staining. Only 5 of 8 poorly differentiated carcinomas were similarly stained. Chen ZM et al., reported that AMACR was positive in 67% of well to moderately differentiated colorectal adenocarcinomas, in contrast to 17% of poorly differentiated carcinomas [30]. Jiang Z et al., also studied 176 colorectal adenocarcinomas and showed that three-fourths of well differentiated and moderately differentiated carcinomas overexpressed AMACR, while the poorly differentiated carcinomas showed a much lower frequency of positivity [31]. In the present study, using gastric samples, AMACR expression was strongest in well differentiated adenocarcinomas compared to moderately or poorly differentiated adenocarcinomas. This result was similar to that observed in colorectal carcinomas in the study by Zhou M et al., [29].

Overexpression of AMACR has been observed in several tumours, most notably prostate and colorectal carcinoma, which have been linked to high fat diets [29]. The exact mechanism by which a high fat diet contributes to tumourigenesis in these organ systems is not clear, but emerging evidence suggests that the PPAR-mediated pathway plays a critical role [21]. AMACR is an enzyme involved in beta-oxidation of branched fatty acids, which can function as a PPAR activator and promote cell growth [32,33]. PPAR gamma expression in human gastric carcinomas and its effect on proliferation of gastric carcinoma cell lines has also been reported [22]. The fact that AMACR is expressed in adenomas and carcinomas in the stomach that is normally unexpressed by real-time PCR raises the possibility that AMACR may play a critical role in the tumourigenesis of the gastric adenoma-carcinoma sequence and be closely associated with the development of early stage intestinal type gastric carcinomas, but not be involved in the progression of carcinomas [15].

Mroz A et al., focused on possible association between AMACR expression and patients' survival. AMACRs prognostic value was assessed in several papers, with mixed results. These included lung, prostate, colon, ovarian, and renal cancers. According to their results, AMACR does not influence survival within the first two years of observation. Its long term impact, however, could not be excluded, as the survival difference almost reached statistically significant level (p-value=0.06). They concluded that AMACR positivity is associated with shorter disease free survival, particularly after the first 22 months of observation [24].

According to Shilo K et al., (n=72) high expression of AMACR in small cell carcinoma of lung showed a better 5-year survival rate [34]. A study by Lin A et al., (n=163) concluded AMACR as a worse prognostic factor in adenocarcinoma of colon [35]. As per Shi X et al., (n=106) AMACR showed no impact on overall survival in cases of colorectal carcinoma [36]. In a study by Rubin MA et al., (n=204) better overall survival was noted in cases of prostatic adenocarcinoma with positive AMACR immunostaining [37]. Worse overall prognosis was shown by Noske A et al., (n=134) and Langner C et al., (n=268) in ovarian carcinoma and urothelial carcinoma, respectively [38,39]. Witkiewicz AK et al., (n=160) studied AMACR immunostaining in invasive and in situ carcinomas of breast and showed a trend towards worse prognosis [40].

In the present study, 15 cases were followed-up for a period of one year of which seven cases died within a period of six months after gastrectomy. These cases showed intense staining with AMACR. Though the number of cases followed-up was not significant, these findings cannot be ignored. The majority of gastric cancer patients have advance stage of the disease at the time of diagnosis. Radical surgical resection has been the main treatment modality for resectable disease [41-43]. However, up to 70% of patients with advanced stage gastric cancer have a relapse and die within five years after resection despite recent improvements in surgical treatment [44]. Recently, use of adjuvant chemotherapy and radiotherapy has led to decreased local and regional relapse rates, thus bringing an improvement in the prognosis of gastric cancers. However, further advances in local tumour control, reduction in metastasis, and minimisation of therapy related toxicity are required to increase the survival rates in patients with gastric cancer. Emerging evidence suggests that identification of more specific targets for combating gastric cancer is the need of the hour.

AMACR may be one such target. Currently, AMACR's role as a potential target for treating gastric cancer seems to be a promising option. However, confirming AMACR'S role requires a thorough understanding of the function of AMACR in gastric tumourigenesis as well as its use as a therapeutic agent. One possible role of AMACR in inducing gastric cancer is via its ability to act as an activator of PPAR-γ, an enzyme that is predominantly expressed in adipose tissue and has an important function in triggering adipocyte differentiation. Thus, AMACR may play a role in the promotion of gastric cancer cell growth through PPAR-γ activation [22].

Limitation(s)

The present study was only for one and a half year and 15 cases could be followed-up for a period of one year. Follow-up of all the cases for a longer period would have enabled us to predict the significance of AMACR as a prognostic marker and also in targeted therapy. Also only the specimens from which adequate tumour tissue could be obtained for IHC staining could be included in the study.

CONCLUSION(S)

IHC expression of AMACR showed a significant association with Lauren's type of gastric cancer and also with Histological grading of differentiation. The expression of AMACR was significantly higher in intestinal type gastric carcinoma and well differentiated histological grading gastric carcinomas. The role of AMACR as a target for treating gastric cancer seems to be promising. Few studies reported AMACR as an adverse prognostic factor and shorter disease free survival period. Further studies are required to establish the role of AMACR as a diagnostic, therapeutic and prognostic tool in gastric malignancies.

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