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Role of p53 Expression in the Progression of Gastric Cancer in the Indian Population

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ABSTRACT

Introduction: Gastric carcinogenesis frequently affects tumor suppressor TP53 gene, resulting in increased expression of p53 protein and mutations towards later stages of Gastric Carcinoma.
Objectives: To analyze p53 protein expression in different stages of gastric cancer to determine if it could be used as a biomarker to allow targeted screening of high risk groups with intestinal metaplasia.
Methods: We retrieved 101 formalin fixed paraffin embedded tissue blocks of histopathology proven Gastric Carcinoma specimens and conducted an immunohistochemical study on a subset of 25 cases. Tumor sections were taken with adjacent normal mucosa. p53 expression was evaluated using immunohistochemical markers. With the observations from the study, analysis of p53 expression in different areas of the mucosa was done.
Result: Thirteen carcinoma cases (52%) expressed p53 protein with a majority of eight (66.7%) cases showing intensity 3. Normal and metaplastic mucosa did not express p53 protein. In dysplastic mucosa, seven (28%) cases showed p53 expression with intensity ranging from 1 to 3. On comparing the data after excluding the p53 negative regions of normal and metaplastic mucosa, there was no difference with statistical significance.
Conclusion: p53 expression is negative in normal and metaplastic gastric mucosa but shows expression in dysplastic and cancer cells. Thus, TP53 mutation is most likely an event towards later stages of carcinogenesis. We are dubious on the ability of p53 to be used as an authentic screening tool at the metaplastic stage to predict progression to carcinoma.

KEYWORDS: Intestinal Metaplasia, Gastric Cancer, p53, Imunohistochemistry

I. INTRODUCTION

Gastric Carcinoma is the fourth most common cancer in the world with annual diagnosis of 1 million patients and mortality of 7,00,000 [1].The high mortality rate is due to advanced stage at diagnosis, limited biomarkers for early detection and lack of systemic screening. Various carcinogenic pathways, for example, Helicobacter pylori infection triggers intestinal metaplasia (IM) as a key precursor lesion of Gastric Carcinoma (GC), usually resulting in Intestinal type GC (IGC) [2].IM is identified histologically by presence of goblet cells, which maybe Type I (Complete) or Type II and III (Incomplete), depending on the morphology of cells and mucin.Type III is mostly associated with the development of GC[3,6].

Gastric carcinogenesis includes various molecular events, one of which involves the tumor suppressor gene, TP53, resulting in increased expression of p53 protein and mutations towards the later stages following the development of GC [4]. Loss of function of the p53 protein can also occur through elevation of its negative regulators like Mdm2 or Mdmx (Mdm proteins) [5], which are seen with wild type of p53 [1]. The expression of p53 protein increases further in incomplete IM samples [7,8].We expected to observe an increment in p53 expression with advancing stages of GC, i.e., from normal mucosa to intestinal metaplasia to dysplasia to GC. The aim of this study is to determine whether p53 protein expression could be used as a biomarker to allow targeted screening of high risk groups with intestinal metaplasia of the stomach for Gastric Carcinoma.

II. METHODS

A. Data collection

We retrieved data of 101 patients who underwent gastrectomy in our institute from 2016 to 2018. From the data 25 formalin fixed paraffin embedded tissue blocks of histopathology proven Gastric Carcinoma specimens were selected for this study. Tumour sections were taken along with adjacent normal mucosa. Immunohistochemistry markers were used to evaluate the expression of p53 in the section. We analyzed p53 expression in different areas of the mucosa including normal mucosa, metaplasia, dysplasia and gastric cancer in a subset of 25 specimens.The study was initiated following review and approval granted by the Institutional Ethics Committee.

B. IHC Scoring of p53 stained sections

IHC was performed according to the method given in the department standard operating procedure (SOP). Nuclear staining of samples were scored as follows: 0(Completely negative), 1+ (10% cells positive), 2+ (10-49% cells positive), 3+ (>50% positive).IHC expression in the normal mucosa, metaplastic epithelium, dysplastic epithelium and cancerous mucosa were assessed separately.

C. Statistical Analysis

Statistical Analysis was performed using the SPSS 16 software. Quantitative data will be expressed by mean and the standard deviation. Difference between means will be determined by non-parametric tests including Kruskal-Willis Test and t test or Mann whitney 'U'test. Qualitative data will be expressed in percentage with confidence interval. Difference between proportions will be assessed by chi square test. $P< 0.05$ is considered statistically significant.

III. RESULTS

A. Demographic Profile

The data collected belonged to patients of diverse demographic background. They were between 25 to 85 years of age. Among the 25 specimens, eight (32%) cases belonged to the age group between 25-50 years of age, twelve (48%) cases belonged to the age group between 50 - 70 years of age and the remaining five (20%) cases were above 70 years of age. The median age was found to be around 55 years of age. Specimens comprised of fourteen (56%) male patients and eleven (44%) female patients with a male to female ratio of 1.2:1.

B. Histopathological Profile

Most common site of gastric cancer was found to be antrum which was seen in fourteen (56%) cases, followed by body of stomach which included eight (32%) cases, fundus had two (8%) cases and gastro esophageal junction had one (4%) case. The specimens ranged from 2cm to 10cm in size. Seventeen (68%) cases were large gastric cancer (size>4cm) while eight (32%) cases belonged to small gastric cancer (size≤4cm) [9]. Histological types included thirteen (52%) diffuse type of GC and twelve (48%) intestinal type of GC. Thirteen (52%) cases were grade III, followed by ten (40%) cases which were grade II and two (8%) cases were grade I. Lymph vessel invasion was seen in thirteen (52%) cases while lymph node involvement was seen in seventeen (68%) cases. On analyzing the survival data, we noticed that sixteen (64%) patients survived, seven (28%) patients succumbed to the disease and we lost follow up on two patients.

C. Analysis of p53 Expression

p53 protein expression was variable in different types of gastric mucosa (Fig:1). The normal and metaplastic mucosa showed negative staining for p53. Analyzing data from the dysplastic cells, we observed that seven (28%) cases showed p53 expression with a mean percentage expression of 37% with intensity ranging from 1 to 3 (Fig: 2). The cancer cells showed further p53 expression which included thirteen (52%) cases with a mean percentage expression of 68.3%, out of a which a majority of eight (66.7%) cases had intensity 3.On comparing the data after excluding the p53 negative regions of normal and metaplastic mucosa, there was no difference with statistical significance.

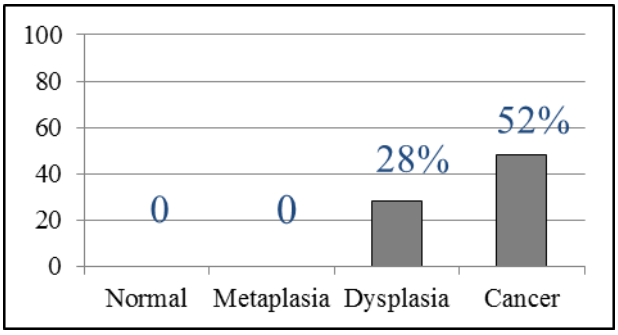

Figure 1 – p53 IHC expression in various types of gastric mucosa.

Among the three age groups, 50-60% cases showed p53 positivity in each group. Male patients exhibited a higher positivity of 57.1% while female patients showed 45.5% positivity. The cancers of gastric antrum expressed 50% positivity followed by the cancers of gastric body which showed 42.9% positivity. All cases of cancers in the fundus and gastro esophageal junction showed p53 expression. Large gastric carcinoma showed a positivity of 52.9% while small gastric cancer noted a positivity of 50%. Diffuse histological type revealed 61.5% positivity in comparison to intestinal type that showed 41.7% positivity. All three grades of tumor manifested around 50% positivity. Lymphovascular invasion and lymph node involvement exhibited around 50% positivity. All stages of the tumor taken expressed around 50-55% positivity.

Figure: 2 – Histopathology and p53 IHC images

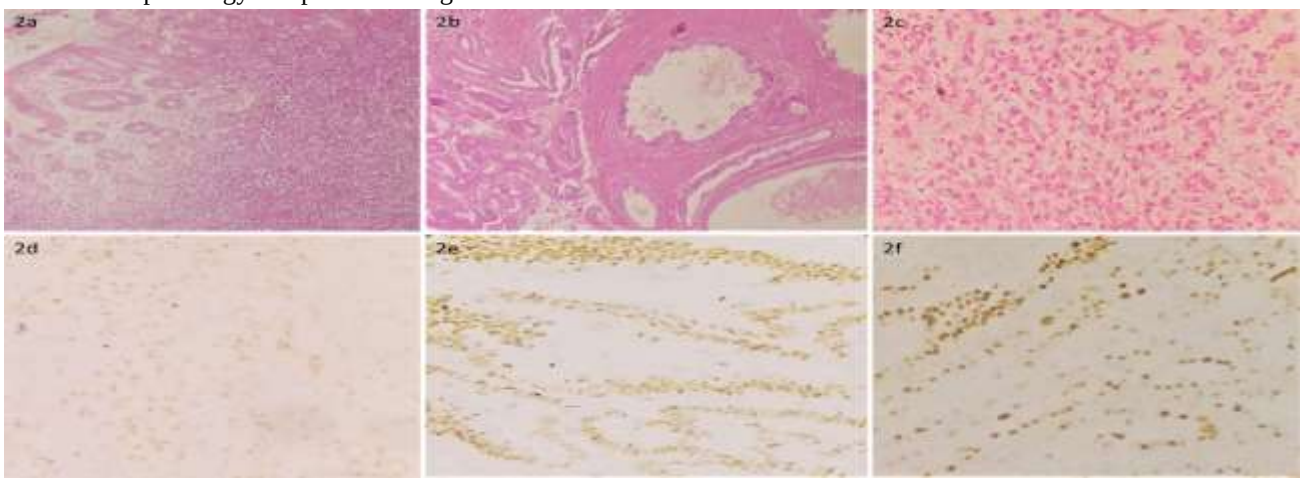

Figure 2- a. Sections from the junction of normal and dysplastic epithelium interface of the gastric mucosa H&E X 40, b. Gastric carcinoma intestinal type showing invasion of the tumor into the muscularis propria H&E X 100, c. Gastric carcinoma diffuse type showing signet cells H&E X 400, d, e, and f. Immunohistochemistry for p53 showing nuclear positivity 1+, 2+, 3+ in the tumor cells respectively.

Patients who survived demonstrated 56.3% p53 positivity, on the contrary, patients who succumbed to the disease revealed only 28.6% positivity.

IV. DISCUSSION

Gastric Cancer is a disease associated with high mortality but its establishment and progression occurs over a long period of time [12,13]. It is multi factorial involving genetics, environment, lifestyle and diet [10]. To enhance prognosis and treatment options it is prudent to get into the molecular make-up of tumor cells to analyze different mutations.TP53 is a key tumor suppressor gene frequently mutated in gastric carcinogenesis [11].

Gastric Cancer develops through a progressive transition from the normal mucosa to metaplastic and dysplastic intermediates, finally approaching carcinoma [12,13]. Most of the cases are diagnosed at an advanced stage attributable to the vague symptoms of presentation which could be as mild as abdominal fullness, leaving us with palliative care as the only treatment. A curative therapy would only be feasible at an early stage of the disease. We thus sort to analyze the progression of gastric cancer and expression of p53 protein. We wanted to investigate its significance in the early carcinogenic pathways, which could then be used in early diagnostic and therapeutic applications.

p53 expression in normal mucosa has rarely been reported which was consistent with our study [14]. Studies in various parts of the world have reported expression of p53 in metaplastic cells ranging from 0 to 42% [7,15,16]. There is a lack of data from the Indian sub-continent on the expression of p53 in metaplastic cells. In our study, we see that metaplastic cells were negative for p53 staining. The expression is dependent on the type of intestinal metaplasia and genetic factors. Other regulator genes like Mdm 2 also have implications on the function of p53 molecule [5]. P53 expression is known to be higher in dysplastic and cancer cells [14]. Our study demonstrated increased expression in dysplastic and cancer cells (28% and 48% respectively), suggesting that p53 mutation could be a late occurring event in carcinogenesis [14]. Further studies could validate the same.

On comparing p53 expression with other parameters, we concluded that there wasn't a significant relationship between age and the marker expression but we noted higher expression among male patients [5,17]. The cancers of gastric antrum showed higher expression in comparison to cancers of gastric body. Though cases of gastric cancer in the fundus and gastro esophageal

junction exhibited p53 expression, the limited number of cases in each category does not allow us to make a definitive conclusion on these types of gastric cancer. p53 expression was equal in small and large gastric cancers, thus being independent of the tumor size [17]. We observed that diffuse type had higher p53 expression which could be one of the factors influencing p53 expression [5,17].

IHC expression of p53 positivity was noted in around half of the cases of grade II and grade III cancers but grade I tumors cannot be interpreted effectively owing to limited cases in the group. p53 positivity was nearly equal among the different stages of GC. From our study, we don't find a significant correlation between p53 expression and the grade or stage of the tumor. Lymphovascular invasion and lymph node involvement did not show a direct variability with respect to p53 expression [17].On the contrary to data from studies in China our study from the Indian population reveals a possible increase in survival with p53 expression[18].

Limitations of our study include the retrospective design and the sample size. Further genetic and immunohistochemical studies on the Indian population on a large scale are required for effective analysis of the same. Analyzing data from our study, we are uncertain of the ability of p53 to be used as a

cost effective and feasible screening tool at the metaplastic stage to predict progression to cancer in the Indian population.

V. CONCLUSION

From our study, we observe major differences in p53 expression in different stages of gastric cancer. We conclude that p53 expression is negative in normal as well as metaplastic gastric mucosa but expresses positivity in dysplastic epithelium and cancer cells, suggesting that TP53 mutation is likely to be a late event in gastric carcinogenesis. Thus, we are dubious on the ability of p53 to be used as an authentic screening tool at the metaplastic stage to predict progression to carcinoma in the Indian population. Further studies on p53 expression and correlation with other demographic and histopathological factors could probably promulgate its role as a potential diagnostic and prognostic tool, aiding in developing novel biological therapeutic modalities.

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