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Research Article

Gastric Signet Ring Cell Carcinoma - Clinicopathological and Molecular Profile in Indian Population

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Introduction

Despite a steady decline in occurrence, gastric cancer is one of the most prevalent and deadly neoplasms in the world [1]. According to GLOBOCAN 2018, stomach cancer is the fifth most prevalent neoplasm and the third most lethal malignancy, accounting for an estimated 783,000 deaths in 2018 [2]. There are five histopathological subtypes of gastric adenocarcinoma, including tubular, papillary, mucinous, poorly cohesive (including signet ring cell carcinoma), and rare variants according to the World Health Organization (WHO) classification [3]. In most parts of the world, the incidence of stomach cancer has been steadily declining over the last several decades [4]. These downward trend can be attributed to the unexpected success in prevention, such as improvements in the treatment of *H. pylori* infection [5]. However, gastric signet ring cell carcinoma (GSRC), a subtype of stomach cancer, is on the rise in Asia, Europe, and the United States, 35-45% of new adenocarcinoma cases [6,7]. Recent studies have shown that gastric signet ring cell carcinoma (GSRC) has poor response to chemo or radiation therapy and it be should be considered a distinct gastric malignant entity [8].

Pathological and molecular sets of GSRC demonstrate different features of poor cohesion and differentiation according to the WHO, Japanese Gastric Cancer Association, and Laurén classifications [9].

There is a scarcity of Indian literature that focuses on clinical, pathological and molecular profile which determines outcomes of GSRC. This study aims to analyse the clinicopathological and molecular profile of GSRC in the Indian population.

Methodology

This study included patients with pathologically identified morphology of Gastric Signet Ring Cell (GSRC) carcinoma between June 2021 to September 2022. This was a hospital-based prospective study.

Data was collected using questionnaire to analyse risk factors, clinical and molecular profile. Prognosis was assessed with the help of imaging scans and telephonic conversations.

Data was analysed by standard statistical method where descriptive statistics was performed, and categorical variables were expressed as percentages whereas continuous variables were expressed as mean.

Results

Clincal profile:

A total of 52 patients were screened out of which 21 patients were included in this study period who had morphology of GSRC amongst which 12 (57.14%) were males and remaining were female. These patients had a mean age of 52 years and 7 (34%) patients of GSRC were less than 40 years of age. 17 (80%) patients presented with locally advanced or metastatic disease. Other patient demographics are as depicted in **table 1**.

Risk factor analysis :

This study indicates the possible risk factors are smoking, chronic atrophic gastric changes, H.pyroli infections. Pylorus and distal stomach involvement as pathology site was also one of these risk factors.

Pathological profile:

At the end of this analysis, 7 (33.33%) were alive for more than one year of which 4 patients survived for more than two years. Three-year OS was seen in 4 (19%) patients.

Molecular characteristics as Comprehensive Genomic Profiling (GCP) was done in six patients of which one patient had ERRBB2 amplification, two patients had ARID1A2 mutation (one patient did not respond to PARP inhibitor while other patient was not treated with PARP inhibitor), one patient had FGFR2 amplification and CCNE mutation was observed in one patient. High MSI was found in one patient who had the longest survival and lived for 8 years. PDL1 was positive in one patient who did not respond to immunotherapy and died after 5 months of diagnosis. CDK6/MET amplification was seen in one patient and low HER 2 expression (HER2-2+, with FISH negative) was found in one patient.

Characteristics	**Patients N (%)**
Age (Mean)	53 years , (range of 18-68)
Gender Male Female	 12 (57.14%) 9 (42.86%)
Advanced/Metastatic disease	17 (80%)

Risk Factors	
H. Pylori infection	3 (14.28%)
Chronic atrophic gastric changes	4 (19.04%)
Smoking history	2 (9.52%)
Secondary malignancy	1 (4.72%)
Family history	1 (4.72%)
Pathology Site	
Pylorus & distal stomach involvement	18 (85.71%)
Intestinal type	3 (14.28%)
Diffuse	8 (38.09%)

Table 1: Patient demographics with Signet Ring Cell Carcinoma

Discussion

The prognosis of GSRC in advanced gastric cancer is controversial. Some reports suggest a worse prognosis, while others suggest that the presence of GSRC in gastric adenocarcinoma is not an independent predictor of prognosis after adjustment for the stage. But in most studies, GSRC was at a more advanced stage, suggesting a more aggressive GSRC phenotype and lower R0 resection rate [17], which could explain the poorer prognosis in some studies. This hypothesis is supported by results from several studies in which GSRC had a worse prognosis [18,19,20]. our study shows 51% of gastric cancer has signet ring morphology which is higher than western data, and median age is 55 years with 30 % belonging to less than 30 years of age. Our data also found that signet ring morphology are more common in distal stomach than proximal stomach and 80% presents with metastatic disease.

Additionally, the research highlights the significance of a thorough genetic profile and MSI status in gastric signet ring cell cancer. Research was done on a very small sample size; larger sample sizes will provide more insight on gastric signet ring cell carcinoma profile which can help in identification of potential target to manage this aggressive carcinoma.

Conclusion

Given that gastric signet ring cell carcinoma has the worst prognosis compared to existing standards of care, it warrants further investigation as a distinct entity. In-depth molecular analysis needs to be carried out in order to determine possible therapeutic targets. Proteomics and single-cell genomics play a key role in identifying distinct molecular and genomic markers in signet cells that may be targets for therapeutic intervention. The study further highlights the significance of MSI status and a thorough genetic profile in gastric signet ring cell cancer. The study used a rather limited sample size; larger sample sizes will provide more information on the management of stomach signet ring cell cancer.

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