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Original Article

Surgery Section

Clinical Significance of Signet Ring Cell Histology in Colorectal Malignancies

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ABSTRACT

Introduction: Signet Ring Cell Carcinoma (SRC) is a histological variant of adenocarcinoma. SRC accounts for 0.5 to 1% of all colorectal malignancies. SRC usually occurs at an early age compared to usual adenocarcinoma. Lymph nodal and peritoneal spread is common and occurs early in the course of colorectal SRC.

Aim: To study clinical significance of signet ring cell histology in colorectal carcinoma.

Materials and Methods: We retrospectively studied 209 cases of colorectal adenocarcinoma in our institute from Jan-2012 to July-2015. All patients in the study were evaluated with colonoscopy except for those presented with intestinal obstruction, as they were taken up for emergency laparotomy. Age and sex of the patients, stage of the disease, segment of the large bowel involved, management and outcomes were studied.

Results: Of 209 patients included in the study, 11 were found to have SRC variant of adenocarcinoma. Out of 198 patients with adenocarcinoma (non-signet ring cell), 111 were male and 87 were female, Out of 11 patients with SRC, 6 were male and 5 were female. Median age of patients with adenocarcinoma is 57 years, while it is 48 years in SRC group. Out of 198 patients with adenocarcinoma, 112 patients underwent surgery of which 7 were palliative procedures, while 9 out 11 patients underwent surgical intervention in SRC group, of which 6 patients underwent palliative procedures

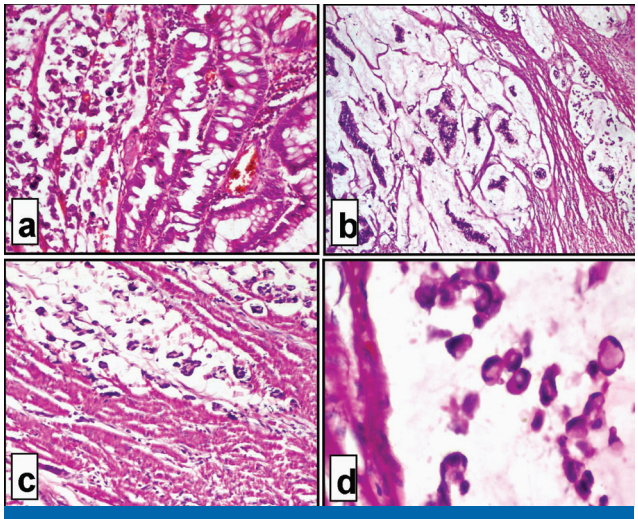
Conclusion: This study signifies that colorectal SRC carcinomas have early age of onset. Advanced stage at the time of presentation and low rates of curative resection due to peritoneal and mesenteric lymph nodal deposits, which contributed to high mortality in colorectal signet ring cell carcinomas.

Keywords: Adenocarcinoma, Mesenteric lymphadenopathy, Metastasis

INTRODUCTION

Majority of colorectal malignancies are adenocarcinomas. There are histological variants apart from usual type of adenocarcinoma, like mucinous adenocarcinoma and medullary carcinoma, SRC adenocarcinoma, small cell carcinoma of undifferentiated type. Signet ring cell carcinoma (SRC) is a histological variant of adenocarcinoma, characterized by accumulation of mucin inside the cells and push the nucleus to periphery giving an appearance of signet ring [Table/Fig-1a-d].

Signet ring cell carcinoma has been defined as the presence of at least 50% of signet ring cells in the pathological specimen, according to WHO classification. SRC accounts for 0.5 to 1% of all colorectal malignancies with male predominance. SRC occurs at an early age compared to usual adenocarcinoma. Some studies shown that more than 50% of colorectal SRCs detected in individuals younger than 40 years [1]. Colorectal SRCs are more common in patients with ulcerative colitis.



[Table/Fig-1a-d]: Shows histology of colorectal signet ring cell carcinoma (HE staining), with abundant mucin and peripherally placed nucleus.

Around 30% of colorectal SRCs occurs in patients with ulcerative colitis [2]. Compared to gastric SRC, colorectal SRCs are less commonly associated with diffuse infiltration of tissues. SRC carcinomas of colon occurs in equal frequency in right and left colon [3]. In colorectal SRC metastases commonly found in lymph nodes, peritoneum and ovaries rather than liver. Before considering primary colorectal SRC, the possibility of metastasis from stomach or breast has to be ruled out, as gastric SRC is more common than colon. Immunohistochemistry helps in differentiating primary colon lesions from metastasis in colon, CK 7 -ve with CK 20 +ve suggestive of primary in large bowel while CK 7 +ve with CK 20 -ve favors a metastasis. Benign signet ring changes may be seen in pseudomembranous colitis and other inflammatory conditions of colon [4].

MATERIALS AND METHODS

This study was conducted in the Department of General Surgery, KMC, Mangalore, India. We retrospectively studied 209 cases of colorectal adenocarcinoma, from Jan-2012 to July-2015. All patients with histopathologically proven colorectal malignancy were included in the study. Ethical committee approval was obtained. All patients in the study were evaluated with colonoscopy except for those presented with intestinal obstruction, as they were taken up for emergency laparotomy. Age and sex of the patients, stage of the disease, segment of the large bowel involved, management and outcomes were studied. Outcomes were analyzed using chi-square test. Patients were followed for a period of six months. Most of the study subjects were from southern Karnataka and Northern Kerala, including districts of Dakshin Kannada, Udupi, Shimoga, Kasargod and Kannur.

RESULTS

Of 209 patients included in the study, 11 were found to have SRC variant of adenocarcinoma [Table/Fig-2]. Out of 198 patients with adenocarcinoma (non-signet ring cell), 111 were male and 87 were female, Out of 11 patients with SRC, six were males and five were females. Median age of patients with adenocarcinoma is 57 years, while it is 48 years in SRC group [Table/Fig-3]. Out of 198 patients with adeno carcinoma, 112 patients underwent surgery, in those seven were palliative procedures, while nine out 11 patients underwent surgical intervention in SRC group, of which six patients underwent palliative procedures because of extensive disease like peritoneal and omental deposits, noted intra-operatively. Complete surgical resection was done only in three patients and one of these three developed recurrence in four months in. Out of 112 patients in the adenocarcinoma group, who underwent surgery, seven presented with signs of intestinal obstruction, while two of the 11 patients presented with intestinal obstruction in SRC group. Out of 112 patients 13 patients died within six months from surgery in adenocarcinoma group, Out of 11 patients in SRC group, eight died within six months from diagnosis, only two survived beyond six months and one patient lost follow- up after surgery [Table/Fig-4].

S. No	Age (Years)	Sex	Clinical Presentation	Part of Large Bowel Involved	Treatment	Outcome
1	49	F	Pain in abdomen and bleeding PR	Ascending colon	Right hemicolectomy	Recurrence after four months of surgery and expired
2	40	M	Bone metastases	Sigmoid colon	Palliative chemotherapy	Expired in three months
3	54	M	Pain in abdomen and loss of appetite	Ascending colon	Palliative resection and Ileo-transverse anastamosis	Expired in four months
4	27	F	Bleeding PR	Rectum	Palliative resection with colo-anal anastamosis	Chest wall metastasis and death after six months
5	39	F	Known case of ulcerative colitis	Caecum and ascending colon	Total colectomy with ileostomy (palliative)	Expired on 9th post op day
6	48	M	Abdominal pain	Caecum and ascending colon	Total colectomy with ileo-anal anastamosis	Completed six cycles of chemotherapy
7	29	M	Intestinal obstruction	Sigmoid colon	Ileostomy (palliative)	Expired after one month
8	49	M	Cholecystitis (metastasis to gallbladder)	Sigmoid colon	Palliative chemotherapy	Lost follow-up
9	70	M	Intestinal obstruction	Sigmoid colon	Transverse colostomy (palliative)	Expired on 3rd post op day
10	40	F	Abdominal pain and weight loss	Ascending colon	Right hemicolectomy	Completed six cycles of chemotherapy
11	48	F	Bleeding PR	Descending and sigmoid colon	Palliative resection with transverse colostomy	Expired in 3 months

[Table/Fig-2]: Shows age, sex, clinical presentation, part of the colon involved, and management of patients with colorectal signet ring cell carcinoma.

	Adenocarcinoma	Signet Ring Cell Carcinoma
No. of Patients	198	11
Male	111	6
Female	87	5
Median Age (years)	57	48
(Inter-Quartile Difference)	(18.25)	(10)

[Table/Fig-3]: Shows number of patients, gender distribution and median age in adenocarcinoma and SRC groups.

	Adeno-carcinoma	Signet ring cell carcinoma	p-value (using chi-square test)
Resectability	105 (112)	3 (9)	<0.001
Peritoneal dissemination	5 (112)	6 (9)	<0.001
Lymphnodal involvement#	36 (105)	7 (7)	0.001
Mortality*	13 (112)	8 (10)	<0.001

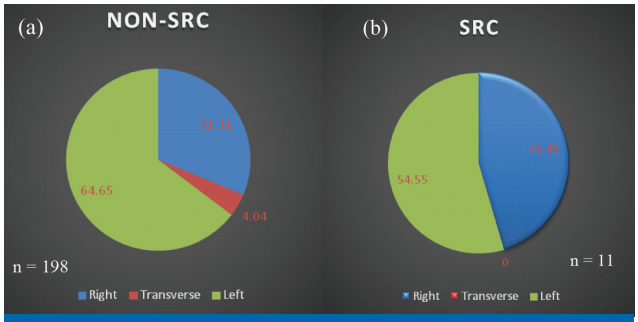
[Table/Fig-4]: Compares resectability rate, peritoneal dissemination, lymphnodal involvement and mortality rate between adenocarcinoma group and SRC group.
#Lymphnodal sampling was not done in cases with intestinal obstruction.
*Mortality at 6 months.

Of the 11 cases with SRC, two cases presented with systemic metastasis in the form of bone metastasis and metastasis to gall bladder and treated with palliative chemotherapy. Lymph nodal sampling was done in seven cases, in all the seven cases lymph nodal metastasis were found. Macroscopic peritoneal deposits were noted in six patients out of nine patients who underwent surgery and none of the patients in SRC group had liver metastasis. One patient had ulcerative colitis who developed SRC carcinoma in ascending colon during follow up. Out of 112 patients in adenocarcinoma group 3 had liver metastasis, five patients had peritoneal metastasis, and one had both peritoneal and liver metastasis. Out of 105 patients who underwent curative resection only 36 had lymphnodal deposits.

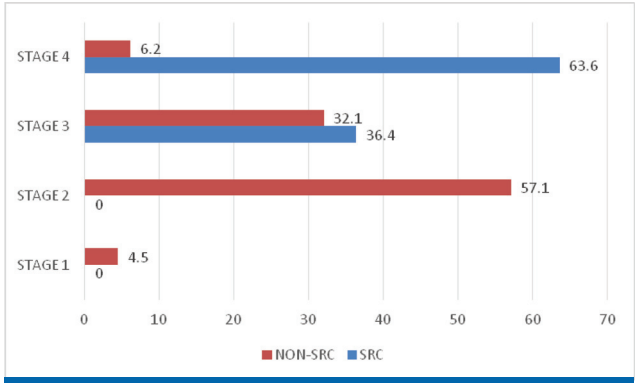
Number of patients at various stages of disease in both the groups were shown in [Table/Fig-5]. Distribution of tumor in different parts of colon in both the groups was shown in [Table/Fig-6a,b]. Frequency of distribution of patients among various stages of disease was shown in [Table/Fig-7].

Stage	Adenocarcinoma	Signet Ring Cell Carcinoma
I	5	0
II	64	0
III	36	4
IV	7	7
Total	112	11

[Table/Fig-5]: Shows number of patients at various stages in adenocarcinoma and SRC groups.



[Table/Fig-6a,b]: Shows frequency of distribution of tumor among right, transverse and left side of colon in adenocarcinoma and SRC groups.
Right- includes caecum and ascending colon
Transverse- transverse colon
Left- descending, sigmoid and rectum



[Table/Fig-7]: Shows frequency of distribution of cases at various stages in adenocarcinoma and SRC groups.

DISCUSSION

More than 96% of SRC carcinomas arise in the stomach, and the rest are seen in lung, colon and to less extent in ovaries. SRC carcinoma accounts for less than 1% of all colon cancers [5]. Laufman and Saphir first described the primary signet-ring cell carcinoma of the colon and rectum, in 1951. Colorectal SRC carcinomas tend to affect predominately young individuals and HNPCC patients [5]. Colorectal SRC develops with equal frequency in right and left colon unlike usual adenocarcinoma which is commonly seen in sigmoid and rectum. Synchronous lesions seen in approximately 14% of patients with colorectal SRC [6].

SRC carcinomas are highly invasive and clinically inapparent, so they diagnosed at advanced stages which contributes for poor prognosis. Some studies have shown that, about 80% of patients with SRC had stage III or stage IV disease at diagnosis [7]. Relatively long period of intramural growth without mucosal penetration may explain delay in clinical manifestations. Full thickness penetration of muscularis

propria and peritoneal deposits are more common than usual adenocarcinoma [6,8,9]. Kim et al., [10] proposed three important factors that contributes to the delay in diagnosis, as well as poor prognosis in cases of SRC carcinomas: (1) The rarity of the tumour; (2) Intramucosal spread of tumor with relative sparing of the mucosa, accounting for minimal symptoms and heme-negative stools; and (3) Radiographic tumour resemblance to inflammatory processes.

Borger et al.,[11] reported that, disruption of E-cadherin/β-catenin complex in signet ring cells causes early dissemination of tumor cells, which correlates with increased T-stage and poor prognosis. Signet ring cells usually appear in loose clusters due to loss of cell adhesions, which explains invasiveness of the tumour and early metastasis. E-cadherin,a cell adhesion molecule, encoded by CDH-1 gene and loss of this cell adhesion molecule is implicated in the development of SRC. Presence of signet ring cells in the histological specimen itself is associated with poor prognosis [12]. Some studies have shown that signet ring histology itself is an independent factor of poor prognosis. SRC carcinoma is more infiltrating tumour with high affinity to lymph nodes and peritoneal surface. SRC is associated with high frequency of Micro Satellite Instability [13]. Colon cancers with high-frequency Micro Satellite Instability (MSI) have in general better survival outcomes. However, in SRC, inspite of increased rates of high-frequency MSI the prognosis is poor suggesting varied carcinogenesis in these tumour [14,15].

Signet ring cells present as singles or in loose clusters due to disruption of cell adhesions. These cells can easily loose contact with surrounding structure and spread diffusely. Peritoneal and lymph nodal spread is relatively common in signet ring cell carcinomas. Distant metastasis is seen in up to 60% of patients at the time of diagnosis [16] so rate of curative resection is less in colorectal SRCs. Pathologically, SRC has unique features compared to that of adenocarcinoma of the colon, which confer aggressiveness to these cells. The signet ring cells are seen floating in abundant extracellular mucin pools either as clusters or isolated cells. These cells have a slightly lower prevalence of K-RAS mutation but a higher BRAF mutation rate as compared to classical adenocarcinoma, and the prognostic implication is unknown [17-19].

In our study group, rate of incidence of SRC was 5.26% which is significantly high compared to similar studies [20]. There is significant difference in the age of presentation between adenocarcinoma and SRC groups (p-value 0.005: Mann-Whitney test). There is no significant gender variation between two groups. Stage of the disease was significantly high in SRC group (p-value <0.001: chi-square tests). No significant difference was noted between two groups in relation to tumour location. Peritoneal dissemination, lymphnodal involvement was more and tumour resectability was less in SRC group. Mortality rate at six months was significantly high in SRC group [Table/Fig-4].

As this was a retrospective study, long term follow-up details were not available. Few patients in the study (86 out of 209) underwent colonoscopy and biopsy on outpatient basis but did not return for follow-up. In all cases of SRC upper GI scopy was done to rule out primary in the stomach except in those presented with intestinal obstruction.

LIMITATIONS

Small sample size, lack of long term follow-up are main limitations of the study. Patients were not evaluated for the other source of primary signet ring cell carcinoma, like lung and ovary, from which metastasis to the colon could be possible.

CONCLUSION

This study signifies that colorectal signet ring cell carcinomas have early age of onset. Advanced stage at the time of presentation and low rates of curative resection due to peritoneal and mesenteric lymph nodal deposits, which contributed to high mortality in colorectal signet ring cell carcinomas.

Further studies with long term follow-up with large sample size are required to support the study and to evaluate the role of screening in family members with colorectal SRC, as early diagnosis may improve the disease outcome.

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