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Signet Ring Cell Colorectal Cancers Portend an Aggressive Biology: A 17-Year Analysis of Operable Colorectal Cancers at a Tertiary Hospital in Pakistan

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Keywords:

Colorectal cancer; Histopathology; Signet ring cell carcinoma; Pakistan; Age; Prognosis

Abbreviations:

SRCC: Signet ring cell carcinoma; CRC: Colorectal cancer; AKUH: Aga Khan University Hospital; SD: Standard Deviation; SEER: Surveillance, Epidemiology, and End Results; CA: classic adenocarcinoma; MAC: mucinous adenocarcinoma

1. Abstract

1.1. Introduction: Primary signet ring cell carcinoma (SRCC) is a rare variant of colorectal cancer, reportedly comprising 0.1%- 2.6% of all colorectal cancers. Due to presentation with symptoms occurring later in the course of the disease, the overall survival is reportedly poorer than that of colorectal adenocarcinoma. Anecdotal evidence suggests that Southeast Asian region has a higher likelihood of having the signet ring cell variant of colorectal cancer. The objective of this study was to determine the overall proportion and histopathological characteristics of colorectal cancer in a Pakistani population across a tertiary care hospital and to ascertain the frequency and presentation of SRCC in colorectal cancer patients.

1.2. Methods: Histopathology reports of the colon and/or rectum specimens diagnosed as primary colorectal carcinoma were identified and reviewed at the Aga Khan University Hospital (AKUH). All the surgical specimens submitted to AKUH from January 2002 to December 2018 were included. Biopsies and histopathological specimens with fragmented bowel, lack of orientation of tissue, and post chemotherapeutic complete resolution of the tumor were excluded.

1.3. Results: Of the 2,662 surgical specimens of colorectal carcinoma identified, 1,708 specimens met the inclusion criteria. The cohort consisted of 62.4% (n = 1065) males, with an overall mean age of 50.41 years (SD = 16.98). Among these patients, 29.5% (n = 504) were 40 years of age or younger, 19% (n = 325) were between the ages of 41 and 50, and 51.5% (n = 879) were older than 50 years ($p<0.001$). The frequency of signet ring cell cancer was found to be 5.4% (n = 92). The histopathological characteristics associated with worse prognosis were significantly associated with the type of tumor. Lymphovascular and perineural invasion, stage, and grade were all significantly higher in SRCC than the other types.

1.4. Conclusion: Pakistani population tends to present with colorectal cancer at a younger age and with poorer prognostic features including higher rates of signet ring cell cancer.

2. Introduction

Colorectal cancer is one of the most common malignant disorders in western populations, whereas cancers of the upper gastrointestinal tract (esophagus and stomach) and liver have predominated in the east. However, during the past few decades, there have been significant changes in the incidence of colorectal cancer in Asian countries, with colorectal cancer being the 3rd most common cancer in both

males and females in Asia [1]. The age-standardized rate of colorectal cancer per 100,000 men is 49.3 in Japan, 24.7 in South Korea, and 35.1 in Singapore, compared with 44.4 in North America and 42.9 in Western Europe [2]. The age-adjusted incidence of rectal cancer as per the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute database from 1975 through 2005 was 16.1 per 100,000 in the United States. Data from the United States suggests that approximately 11% of colon cancer and 18% of rectal cancer occur in individuals younger than age 50 [3]. Interestingly, a rapid increase in colorectal cancer incidence rate in economically transitioning countries has been recently reported in the literature [4] and has been attributed to a change in the dietary habits and physical activity patterns superimposed on genetic predisposition.

The incidence of early-onset colorectal cancer is approximately 7% of the total colorectal cancer population in the West [5], however, the problem has been reported to be of a much greater magnitude in several Asian and African countries [6-7]. Similarly, half of the incident cases of colorectal cancer in the Pakistani population as reported by Bhurgri et.al has been estimated to be in young patients [8]. From this, coupled with the fact that greater than 80% of the Pakistani population is younger than 40 years [9], it can be estimated that the "at-risk" population for early-onset colorectal cancer in countries like Pakistan is much higher than the rest of the world.

These colorectal cancers are more likely to be poorly differentiated, have mucinous and signet ring features, and present at advanced stages The majority of detailed analyses are based in North America and Europe. The results of these meta-analyses and several other studies indicate that sporadic early-onset colorectal cancer is rare in the developed countries. On the other hand, early-onset colorectal cancer is far more common in third-world countries [10]. A study conducted at the Aga Khan University Hospital by Zahir et.al revealed a 32% prevalence of sporadic early-onset colorectal cancer, of which 21 % was SRCC, which is much higher than that suggested by the western data [11-12]

Primary signet-ring cell carcinoma is a rare variant of colorectal cancer, reportedly comprising 0.1%-2.6% of all colorectal cancers [13]. Clinical symptoms tend to occur late in the course of signet ring cell carcinoma. The disease is usually detected at an advanced stage [14], and the overall survival rate is reported to be poorer than that of colorectal adenocarcinoma [15-16]. These cancers tend to display more aggressive behavior and have a poor prognosis. This warrants early screening, diagnosis, and prompt treatment [17].

In the Southeast Asian region, it is observed that younger patients presenting with colorectal cancer show a greater tendency of having the signet cell variant. This study aims to determine the overall proportion of signet ring cell carcinoma and to report the histopathological characteristics of colorectal cancer in the Pakistani population. A further step will be to plan a multicenter prospective evaluation of genetic and epigenetic factors that play a role in the early onset of colorectal cancer and the development of the signet cell variant.

3. Methodology

The study was conducted at the Aga Khan University Hospital (AKUH) in Karachi, Pakistan. Exemption from the Ethics Review Committee of AKUH was obtained before the commencement of the study. The histopathology reports of the colon and/or rectum specimens diagnosed as primary colorectal carcinoma were identified through Index and Coding by the department of Hospital Information Management System and Integrated Laboratory Management System and reviewed. These included all the surgical specimens submitted to AKUH from January 2002 to December 2018. Biopsies and histopathological specimens with fragmented bowel, lack of orientation of tissue, and post chemotherapeutic complete resolution of the tumor were excluded.

Demographic and histopathological data were recorded from patient charts. These included age at diagnosis, gender, previous history of chemotherapy, and tumor characteristics namely the histopathological type, location, TNM stage, grade, lymphovascular and perineural invasion, margin, and lymph node involvement. The circumferential margin was considered involved if tumor cells were found on or <1mm away from the margin. The tumors were divided into four different groups based on histology: classic adenocarcinoma (CA), mucinous adenocarcinoma (MAC), and signet ring cell cancers. The fourth category of rare tumors included the infrequent subtypes, squamous cell, adenosquamous, neuroendocrine, and clear cell carcinoma. Tumors that contained only a component of signet ring cells were excluded from the signet ring cell cancer group.

The data was analyzed using SPSS® version 22.0 for Windows. Continuous variables were reported as mean and standard deviation and median and interquartile range. Statistical tests used include t-test, Kruskal Wallis H test, Chi-square test for independence, Fisher's exact test, and one-way analysis of variance (ANOVA) with posthoc pairwise comparison using Bonferroni correction. A p-value of < 0.05 was considered statistically significant.

4. Results

A total number of 2,662 surgical specimens of colorectal carcinoma were identified between January 2002 and December 2018, out of which 1,708 specimens met the inclusion criteria and were used in the study. The cohort consisted of 62.4% (n = 1065) males and 37.6% (n = 643) females, with an overall mean age of 50.41 years (SD = 16.98). Mean age for males was 51.02 (SD = 16.75), and that for females was 49.40 (SD = 17.32), p = 0.057. Among these patients, 29.5% (n = 504) were 40 years of age or younger, 19% (n = 325) were between the ages of 41 and 50, and 51.5% (n = 879) were older than 50 years.

The frequency of signet ring cell cancer was found to be 5.4% (n = 92). All of these cancers were poorly differentiated at the time of diagnosis and had the highest frequencies of lymphovascular (55.4%) and perineural involvement (52.2%). The most commonly diagnosed cancer was adenocarcinoma, which made up 74.9% (n = 1,279) of

all the colorectal cancers. Mucin secreting adenocarcinoma was the second most common, comprising 18.7% (n = 319) of the tumors, whereas rare subtypes made up the remaining 1.1% (n = 18). Of these, neuroendocrine tumors were the most frequent (n = 15) while the remaining three types were seen only in one specimen each.

The most common tumor site was the colon, with 81.2% (n = 1387) of all specimens being colonic. 13.8% (n = 235) of the tumors were found in the rectum, 4.7% (n = 80) were found at the rectosigmoid junction, and 0.4% (n = 6) were bifocal tumors, found in both the colon and rectum. Table 1 shows the characteristics of the tumors.

Table 1: Histopathological characteristics of the colorectal cancers

Lymphovascular invasion, n (%)	
1. Yes	452 (26.5)
2. No	1136 (66.5)
3. Indeterminate	120 (7.0)
Perineural invasion, n (%)	
1. Yes	410 (24.0)
2. No	1263 (73.9)
3. Indeterminate	35 (2.0)
Lymph nodes received, median (IQR)	19 (15)
Lymph nodes involved, median (IQR)	1 (4)
Circumferential margin involved, n (%)	239 (14.0)
Proximal margin involved, n (%)	9 (0.5)
Distal margin involved, n (%)	28 (1.6)
T, n (%)	
1. Tis	2 (0.1)
2. T1	13 (0.8)
3. T2	181 (10.6)
4. T3	1218 (71.3)
5. T4	294 (17.2)
N, n (%)	
1. N0	744 (43.6)
2. N1	463 (27.1)
3. N2	487 (28.5)
4. Nx	14 (0.8)
M, n (%)	
1. M1	3 (0.2)
2. M2	50 (2.9)
3. Mx	1655 (96.9)
Grade, n (%)	
1. Well-differentiated	126 (7.4)
2. Moderately differentiated	1145 (67.0)
3. Poorly and undifferentiated	437 (25.6)
Neoadjuvant chemotherapy received, n (%)	
1. Yes	51 (3.0)
2. No/Don't know	1657 (97.0)

a: Including <1mm; b: Excluding <1cm; c: Excluding <1cm

The mean age of patients with SRCC at the time of surgery was 11 years (95% CI = -15.35 to -6.67) less than that of patients with adenocarcinoma, $p < 0.001$, and 7.11 years (95% CI = -11.87 to -2.36) less than those with mucinous adenocarcinoma, $p = 0.002$. Additionally, patients with mucinous adenocarcinoma were on average 3.89 years (95% CI = -6.41 to -1.38) younger at the time of surgery than patients with adenocarcinoma, $p = 0.001$. Table 2 shows the mean age at diagnosis for the various tumor types.

The histopathological characteristics associated with worse prognosis were significantly associated with the type of tumor. Age categories had a significant association with different histological types of cancer ($p < 0.001$) with the prevalence of SRCC being 9.7% in those aged ≤ 40 years with a male predominance (64.1% vs. 35.9%, $p = 0.012$). Lymphovascular and perineural invasion, stage, and grade were all significantly higher in SRCC than the other types. The number of lymph nodes involved in SRCC was significantly higher than in adenocarcinoma (9 vs. 0, $p < 0.001$), and mucinous adenocarcinoma (9 vs. 2, $p < 0.001$). All the cases of SRCC were poorly differentiated whereas other histological subtypes were also well differentiated or moderately differentiated ($p < 0.001$). The difference between CA and MAC was also significant, $p < 0.001$. A comparison of other relevant tumor characteristics between the different histological types of cancer is shown in Table 3.

Table 2: Mean age at the time of diagnosis

Tumor histology	Mean age in years (std. deviation)
Adenocarcinoma	51.67 (16.43)
Mucinous adenocarcinoma	47.74 (17.54)
Signet ring cell	40.66 (18.54)
Rare tumors	57.00 (15.53)

5. Discussion

The higher incidence of colorectal cancer in men as compared to women that has been documented in different populations [19-21] was also identified in our study population. It has been hypothesized that the increased vulnerability in men could be due to multiple behavioral and genetic factors, such as increased intake of red meat, alcohol, and tobacco smoking. [23-25]. Also implicated in the pathogenesis of colorectal cancer is the obesity-related metabolic pathways that are thought to be more heavily influenced by visceral abdominal fat that men tend to accumulate, more of as compared to women, in whom subcutaneous fat is more common [26].

In our sample, almost half of the patients were > 50 years old. Of the remaining cases, almost 60% of the patients were < 40 years of age. These observations are in line with the US, where using SEER data, a steady increase in the incidence of colon and rectal cancer in the younger demographic of age (20 -49 years) was identified [27]. For colon cancer in this group, they reported a rate increase of 1.3% annually between 1996 and 2016. For rectal cancer, the increase was 2.3% annually since 1991. The same data set indicated a steady decline in incidence rates of colorectal cancer in the 50 and older age

group. This alarming trend of increasing rates of CRC in the younger population in America, Canada, and Australia are well proven [28-30]. These shifts have informed modifications in the screening guidelines of the American Cancer Society, lowering the recommended age for screening to 45 years [31].

Our review indicates adenocarcinoma to be the most common colorectal cancer histology. According to the WHO classification of tumors of the digestive system, more than 90% of colorectal carcinomas originate from the epithelial cells of the mucosa lining the gastrointestinal system and are thus adenocarcinomas [32]. We report a higher percentage of the well-differentiated tumor on grading (7.4%) as compared to a study conducted in a population in a similar geography. That study was conducted at a tertiary care hospital by Patil et al and reports 2.6% of CRC to be well-differentiated [33].

Five percent of our study population was found to have signet ring cell morphology. Of the 92 SRCC tumors, 53% (49) were in patients aged ≤ 40 years. This is very different from the reported incidence in Western populations. Nitsche et al. in a longitudinal cohort of 3,479 patients from Germany reported a 0.9% prevalence [37]. Another cross-sectional analysis of 131 patients aged 45 years or below from Pakistan identified 28(21.3%) patients with SRCC, as compared to 9.7% in the < 40 years' age group in our study [11]. However, the overall prevalence of SRCC from the handful of previous small sample studies available from Karachi has reported a frequency of 3-5% [38, 39], while one from Lahore, another large metropolitan city in a different part of the country, has reported rates as high as 11% [40].

The signet-cell variant of CRC is historically associated with poorer prognostic factors. We identified a higher proportion of lymphovascular invasion (55.4 %), perineural invasion (55.2 %), and stage at presentation in the signet ring cell cancers when compared to the other histologic subtypes (Table 3).

All tumors with signet ring cell carcinoma were poorly differentiated. These tendencies have been documented by other investigators. A study based in South Korea found that signet-ring cell cancers presented at higher stage (III/IV, 80.9 percent) more often than mucinous (52.8 percent) and adenocarcinoma (49.5 percent), and had worse tumor grade (high grade: signet-ring cell, 73.5 percent; mucinous, 20.9 percent; adenocarcinoma, 17.5 percent) [34]. While they found the frequency of signet ring cell carcinoma to be higher than that in the western population (1-2%) [35], literature from India reports a considerably greater prevalence of signet ring cell carcinoma, ranging from 11.4 to 13.5 percent [36].

Our audit is the largest single-center audit of 1,708 specimens with colorectal cancer from across Pakistan. Approximately one-third of the specimens received at our center belonged to patients who were younger than 40 years of age. Current screening guidelines do not cater to this population. There is a need for further understanding of unique population-based risk factors. This information can then be used to inform specific screening and diagnostic algorithms. For example, in this population single flexible sigmoidoscopy for screening may be of benefit and can be evaluated for cost–benefit analysis. However, in view of the limited resource allocation for healthcare in Pakistan, strengthening symptom-based algorithms for the diagnosis of CRC must be a priority.

Table 3: Comparison of characteristics between the different histological types of cancer

	Adenocarcinoma, n (%)	Mucinous adenocarcinom, n (%)	Signet ring cell, n (%)	Rare tumors, n (%)
Age categories				
1. ≤ 40	337 (26.3)	114 (35.7)	49 (53.3)	4 (22.2)
2. 41-50	245 (19.2)	65 (20.4)	15 (16.3)	0 (0.0)
3. > 50	697 (54.5)	140 (43.9)	28 (30.4)	14 (77.8)
Gender				
Male	776 (60.7)	222 (69.6)	59 (64.1)	8 (44.4)
Female	503 (39.3)	97 (30.4)	33 (35.9)	10 (55.6)
Tumor location				
1. Colon	1031 (80.6)	265 (83.1)	73 (79.3)	18 (100.0)
2. Rectum	178 (13.9)	41 (12.9)	16 (17.4)	0 (0.0)
3. Rectosigmoid	65 (5.1)	12 (3.8)	3 (3.3)	0 (0.0)
4. Bifocal	5 (0.4)	1 (0.3)	0 (0.0)	0 (0.0)
Lymphovascular invasion				
1. Yes	301 (25.2)	92 (31.3)	51 (62.2)	8 (47.1)
2. No	894 (74.8)	202 (68.7)	31 (37.8)	9 (52.9)
Perineural invasion				
1. Yes	293 (23.3)	63 (20.3)	48 (53.3)	6 (35.3)

2. No	962 (76.7)	248 (79.7)	42 (46.7)	11 (64.7)
Lymph nodes received, median (IQR)	19 (14)	20 (14)	21 (22)	18 (12)
Lymph nodes involved, median (IQR)	0 (3)	2 (7)	9 (12)	2 (7)
Circumferential margin				
1. Involved	143 (11.2)	56 (17.6)	36 (39.1)	4 (22.2)
2. Uninvolved	1136 (88.8)	263 (82.4)	56 (60.9)	14 (77.8)
T				
1. Tis	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
2. T1	12 (0.9)	1 (0.3)	0 (0.0)	0 (0.0)
3. T2	163 (12.7)	14 (4.4)	3 (3.3)	1 (5.6)
4. T3	931 (72.8)	222 (69.6)	50 (54.3)	15 (83.3)
5. T4	171 (13.4)	82 (25.7)	39 (42.4)	2 (11.1)
N				
1. N0	631 (49.3)	102 (32.0)	4 (4.3)	7 (38.9)
2. N1	353 (27.6)	94 (29.5)	15 (16.3)	1 (5.6)
3. N2	284 (22.2)	120 (37.6)	73 (79.3)	10 (55.6)
4. Nx	11 (0.9)	3 (0.9)	0 (0.0)	0 (0.0)
Grade				
1. Well-differentiated	114 (8.9)	10 (3.1)	0 (0.0)	2 (11.1)
2. Moderately differentiated	960 (75.1)	180 (56.4)	0 (0.0)	5 (27.8)
3. Poorly differentiated	204 (16.0)	129 (40.4)	92 (100.0)	11 (61.1)

a: Tumors present in both colon and rectum; b: Including <1mm

6. Limitations

There is a possibility of referral bias. As our data were collected from histopathological reports of tumor specimens, the majority of which were collected at other hospitals, we could not differentiate between hereditary and sporadic cases of colorectal cancer. We were unable to capture data related to dietary and other risk factors (obesity, smoking status, and ethnicity) or survival data.

7. Conclusion

Large scale data from Pakistan is scarce and most prevalence data comes from small single-institution studies. Significant variations exist in these studies from different parts of the country. However, all data suggest that like other similar populations, the Pakistani population tends to present with colorectal cancer at a younger age and with poorer prognostic features including higher rates of signet ring cell cancer. Limited screening programs and lack of a national database are major areas for improvement required to address the burden of CRC in the population.

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