Primary Signet-Ring Cell Carcinoma of the Colon and Rectum

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PURPOSE: Colorectal signet-ring cell carcinoma (SRCC) is uncommon; discordant data have been previously reported about clinicopathologic features. Thirty-four cases of primary colorectal SRCC were retrospectively reviewed to clarify controversies. METHODS: Primary colorectal SRCC was diagnosed when the following criteria were satisfied: 1) the tumor was primary; 2) histologic material was adequate; 3) signet-ring cell represented more than 50 percent of the cancer. RESULTS: We identified 34 cases (1.1 percent) of 2,995 consecutive large bowel cancers collected at the Institute of Anatomic Pathology of Florence between 1985 and 1993. Patients ranged in age from 31 to 89 (mean, 63.5; median, 65) years; 19 were male, and 15 were female (male:female = 1.3:1). Fifteen tumors were located in the proximal colon, 11 in the rectum, and 8 in the distal colon. The gross shape was infiltrative in 24 cases and exophytic in 10; only 6 cases (17.6 percent) showed features of linitis plastica. Most cancers (61.8 percent) were Stage C, 29.4 percent were Stage B, and distant metastases were present in only three cases (8.8 percent). No Stage A case was found. Prognosis was extremely poor, and overall five-year survival rate was 9.1 percent. Survival was influenced significantly by tumor stage ($P < 0.01$). CONCLUSIONS: Comparison of our data with the literature showed many differences that could be related to different applied diagnostic criteria. We underlined the importance of histology as reproducible criterion for diagnosis of primary colorectal SRCC. [Key words: Colorectal carcinoma; Signet-ring cell; Clinicopathologic features]

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Signet-ring cell carcinoma (SRCC) is a tumor composed predominantly[1] of cells the nuclei of which are peripherally pushed by abundant intracytoplasmic mucins, mainly of the neutral type.[2] This form of cancer is especially uncommon in the colon and rectum. Since the first description by Laufman and Saphir,[3] to the best of our knowledge, another 211 cases have been reported. It is often found in the stomach and less frequently in other organs (pancreas, breast, gallbladder, urinary bladder). Thus before diagnosing primary colorectal SRCC, a secondary involvement of the large bowel must be accurately excluded.[4, 5]

Despite such clear and restrictive diagnostic criteria and the relatively small number of reported cases, the clinicopathologic features of colorectal SRCC are greatly different in the literature, and it is not easy to recognize a uniform pattern of this tumor. In an effort to clarify the controversies, we reviewed thirty-four cases of primary colorectal SRCC and compared clinicopathologic characteristics with previously reported series.

MATERIALS AND METHODS

Between January 1985 and December 1993, 2,995 consecutive large bowel resection specimens for cancer were collected at the Institute of Anatomic Pathology of the University of Florence. Age and sex of the patients, clinical presentation, and site, size, and gross features of tumors were recorded. All tissue samples were fixed in 10 percent buffered formalin, embedded in paraffin, cut at 5 μm, and stained with hematoxylin and eosin. Histologic sections and the report of each tumor were reviewed by the same pathologist (LM) to identify signet-ring cell carcinoma.

The following criteria were applied in diagnosing primary colorectal SRCC: 1) the presence of another primary cancer was excluded; 2) histologic material was adequate, and an average of six slides were examined per tumor; 3) signet-ring cells represented more than 50 percent of neoplastic cells. Site, gross shape, and dimension of the tumor identified as SRCC were retrospectively defined from the original report. With regard to cancer location, three anatomic sites were considered: proximal colon (cecum, ascending colon, hepatic flexure, and transverse colon), distal colon (splenic flexure, descending, sigmoid, and rectosigmoid colon), and rectum.

SRCC was classified macroscopically in two groups: exophytic and infiltrative. The first group showed a gross shape that was mainly exophytic, the latter was macroscopically nonexophytic and comprised infiltrative tumors, ulcer-infiltrating tumors, and diffusely infiltrating cancers ("linitis plastica"). Regarding size, tumors less than or 5 cm in diameter and tumors with a diameter greater than 5 cm were distinguished.

All cases of SRCC were restaged by Dukes system

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modified by Turnbull *et al.*[6]: Stage A = cancer limited to bowel wall, Stage B = cancer with extra mural spread, Stage C = presence of lymph-node metastasis, and Stage D = presence of distant metastasis. Survival was calculated using Kaplan-Meier life tables; differences were evaluated using the log-rank test.

RESULTS

Thirty-four cases (1.1 percent) of primary colorectal SRCC were identified from 2,995 consecutive large bowel cancers. There were 19 male patients and 15 female, with a sex ratio of 1.3:1; mean age was 63.5 (range, 31–89, with two patients younger than 40) years, and the median age was 65 years (Fig. 1).

No patients had risk factors[7] such as ulcerative colitis, Crohn's disease, familial adenomatous polyposis, prior irradiation, or ureterosigmoidostomy.[8] The most common symptom was change in bowel habits (85 percent), followed by abdominal pain (75 percent), and rectal bleeding (60 percent). The average duration of symptoms was 3.2 months before surgery.

Location, gross shape, and size of SRCC are summarized in Table 1. Most tumors were Stage C (Table 2). Overall five-year survival rate for 33 cases (one patient was lost at follow-up) was 9.1 percent. Survival was significantly influenced by tumor stage ($P < 0.01$; Fig. 2).

DISCUSSION

Signet-ring cell carcinoma is a rare form of colorectal cancer, yet the referred data concerning frequency, age, sex, site of location, pathologic features, and prognosis of this tumor are extremely variable. Reported frequency varies widely from 0.2[9, 10] to 2.4 percent[11] of ordinary large bowel cancer but was much higher in some people: 14.2 percent in those from Jordan[12] 18.5 percent in young Lebanese.[13]

In the present study frequency was 1.1 percent.

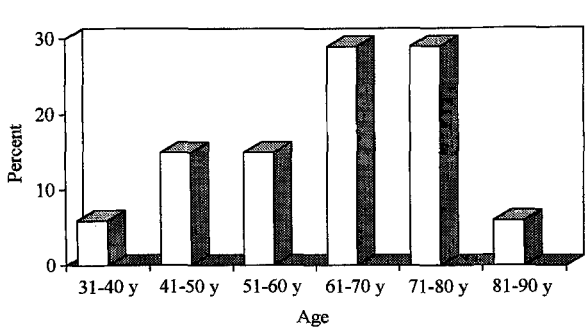

Figure 1. Age distribution of primary colorectal signet-ring cell carcinoma. y = years.

These differences may reflect some diverse etiologic influences such as dietary habits, other environmental factors,[7, 12, 14] or other unknown reasons, but they could also be related to different applied diagnostic criteria. In many studies diagnostic criteria are not well defined or are subjective.[3, 5, 11–13, 15, 16] Moreover, some authors[5, 17, 18] have used macroscopic features of the tumor as a guideline for diagnosis and considered linitis plastica as synonymous with SRCC. Surely it has been well demonstrated in certain cases, but not all SRCCs exhibited this macroscopic feature. Nakahara *et al.*[19] found that only 20 percent of cases of colorectal linitis plastica are caused by SRCC. More recently Shirouzu and colleagues[20] observed that 16.6 percent of colorectal linitis plastica are true SRCC; in the remaining cases signet-ring cells represented only a portion of the cancer. Moreover, Connelly *et al.*[21] first documented that SRCC is more often exophytic than expected.

In the present report 29.4 percent of cases were exophytic, and only 17.6 percent of cancers showed features of linitis plastica. This confirms that this tumor is macroscopically heterogeneous and that the gross shape cannot be considered a valid parameter for diagnosis of SRCC. Thus, we believe, in accordance with World Health Organization directives,[1] that the histologic criterion (with typical signet-ring cells constituting more than 50 percent of the neoplasia) is the most satisfactory for diagnosis of SRCC, under the condition that an adequate number of tumor sections are available. Only in some studies has this criterion been used.[21–25]

Mean age of our patients was 63.5 years, and median age was 65 years. We found this tumor in a wide variety of ages; however, most of our patients (64.7 percent) were older than 60 years (Fig. 1). Only two patients (5.9 percent) were younger than 40 years.

Conversely, some authors[7, 9, 24–28] indicated that SRCC arises most frequently before 40, especially in some people.[13, 14, 27, 29] In other large series the mean age varied from 51[21] to 71[22] years. Truly any age can be affected; Hamazaki *et al.*[30] described a case in a 6-year-old child, and we found a case in an 89-year-old man; however, most reports indicate that SRCC arises more frequently between 50 and 60 years of age. In our series the age of incidence was higher than previously reported.

It has been documented that SRCC is slightly more prevalent in men[17, 20, 25] than in women and that there is no significant difference in incidence between sexes.[15, 21, 31] In accordance with this, we found a sex

Table 1.
Primary Signet-Ring Cell Carcinoma of Colon and Rectum

Location	No.	(%)	Gross Shape	No.	(%)	Size	No.	(%)
Right colon	15	(44.1)	Exophytic	10	(29.4)	≤5 cm	12	(35.3)
Left colon	8	(23.5)	Infiltrative	24	(70.6)*	>5 cm	22	(64.7)
Rectum	11	(32.4)						
Total	34	(100.0)	Total	34	(100.0)	Total	34	(100.0)

* Six cases of linitis plastica.

Table 2.
Five-Year Survival Rate by Tumor Stage

Dukes Stage	Patients		DOD at Five Years*	
	No.	(%)	No.	(%)
B	10	(29.4)	7/10	(70.0)
C	21	(61.8)	20/20†	(100.0)
D	3	(8.8)	3/3	(100.0)
Total	34	(100.0)	30/33†	(90.9)

* DOD = dead of disease.
† One patient was lost to follow-up.

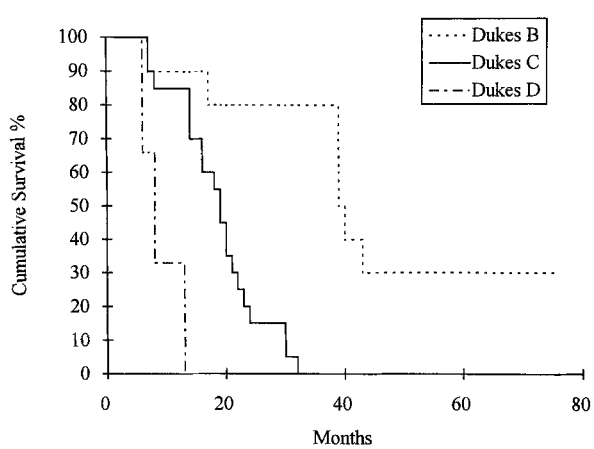

Figure 2. Primary colorectal signet-ring cell carcinoma. Actuarial survival curves by Dukes stage. Differences are statistically significant ($P < 0.01$).

ratio (male:female) of 1.3:1. Some authors, however, demonstrated a clear female predominance.[5, 12, 23, 24]

With regard to site, most reported cases were localized exclusively in the rectum, whereas Halvorsen and Seim[22] found a strong right-sided predominance and Connelly and colleagues[21] showed a similar distribution between the right colon and the rectum and found that SRCC can also be present in the left colon. Our cases occurred prevalently in the right colon, but all sites were involved (Table 1).

In all studies, there is complete agreement concerning one point, the advanced stage of diagnosis of SRCC. Only 1 of 215 previously reported cases was found in Dukes Stage A,[31] whereas most patients (from 60 to 100 percent) developed lymph node metastasis. Distant metastases, especially in the liver, are not common,[7, 19–21, 24] but spread through the peritoneal cavity is frequent[4, 11, 16, 17]; ovarian metastases have been described.[17, 18] Our study confirms these data: we found no patients with Stage A, 29.4 percent of cases with Stage B, 61.8 percent with Stage C, one patient with liver metastasis, and two patients with ovarian metastasis (Table 2).

SRCC is considered a tumor with a poor prognosis, but overall survival at five years varies from 0[23] to 50 percent[22] of patients. However, studies with a large number of cases showed a five-year survival rate in 13[25] to 36 percent[21] of cases. Some authors[21, 24, 31] suggested that survival of SRCC is similar to ordinary colorectal cancer; others[15, 22, 23, 25, 26] confirmed a worse prognosis, which is related to delayed diagnosis.

In our series the overall five-year survival rate was 9.1 percent, with a median survival of 20 months. We found a better survival rate, 30 percent at five years, for patients with Stage B, whereas no patients with Stages C or D were alive at five years (Table 2). All patients with Stage C or D died of disease within two or three years. Median survival was 39 months for Stage B, 19 months for Stage C, and 9 months for Stage D; these differences are statistically significant ($P < 0.01$; Fig. 2).

Clinicopathologic features of primary colorectal SRCC described in the present study can be summarized as follows: 1) SRCC represents 1.1 percent of colorectal cancer, 2) any age can be affected; however, it is rarely present in young patients, and most of our patients are older than sixty years, 3) all colorectal sites are involved, 4) macroscopic features are variable, and linitis plastica is less common than expected, 5) SRCC is diagnosed frequently in the advanced stage, but distant metastases are rare, and 6) prognosis is extremely poor, but Stage B tumors show a better survival.

These findings seem to be in complete agreement with some reports and in striking conflict with others.

Significance of this disagreement could be attributed to the relatively small number of cases in many series, or it could represent a true variability of this tumor.

We believe, however, that selection of diagnostic criteria is a crucial point to accurately define SRCC and to compare different series. We would also like to emphasize the importance of evaluating histologic features as reproducible criterion for diagnosis of primary colorectal SRCC.

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