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RARE PRESENTATION OF SIGNET CELL ADENOCARCINOMA IN VICENARIAN: A CASE REPORT & LITERATURE REVIEW

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Abstract:

Colorectal cancer (CRC) remains a significant contributor to cancer-related mortality, posing diagnostic and management challenges. Despite an overall decrease in CRC incidence, there has been an alarming rise in cases among young adults and adults. CRC, among various histopathological subtypes, signet ring cell carcinoma (SRCC) is comparatively infrequent but shows a higher prevalence in adults compared to older individuals. This subtype displays distinctive histological features, unique clinical characteristics, and unfortunately, a grim prognosis. Here, we present a primary case of signet ring cell adenocarcinoma located in the rectum, affecting a male of 29-year-old. The rare presentation and tumor's location in these cases underscore the need for further investigation and research. We have also conduct a comprehensive literature review pertaining to metastatic SRCC, shedding light on significant findings in this area. This underscores the critical role of collaboration between clinicians and pathologists, emphasizing the importance of thorough histopathological, immunohistochemical, and molecular analyses. Such analyses serve as valuable tools for guiding investigations and facilitating informed management decisions.

Keywords: *Signet ring cell carcinoma, colorectal cancer, grim prognosis, rectum*

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INTRODUCTION:

Statistics in 2023 (United States) shows that colorectal cancer (CRC) is the 3rd most abundant diagnosed malignancy. Nationally and in each state, CRC ranks among the top cancer diagnoses. In 2023, it is projected about 153,020 new cases of CRC will be diagnosed. Unfortunately, 52,550 patients are expected to lose their lives due to CRC in 2023 [1]. These statistics emphasize the significance of CRC as a major health concern and underscore the importance of early detection and effective treatment efforts.

With abundant intracytoplasmic mucin, signet ring cell carcinoma (SRCC) is a frequently diagnosed subtype in cancer of stomach; however, it is considered a sporadic pathological variant within CRC. In fact, SRCC represents only 1% of all types of pathological variants observed in rectal cancer cases [2]. The SRCC is often allied with more aggressive behavior, a higher likelihood of involvement of lymph node, and a generally bad prognosis, particularly when found in advanced stages of CRC [3].

Several consistent findings have emerged from the analysis of clinicopathological characteristics in patients having early-onset CRC (those under 50 years of age). These findings indicate that the occurrence of CRC is more prevalent among younger patients [4,5].

Due to its low incidence, the SRCC has only been sporadically assessed in a few cases only. However, it is noteworthy that SRCC is frequently diagnosed at an advanced stage and is associated with a less favorable diagnosis in comparison with common adenocarcinoma (CAC) and mucinous adenocarcinoma (MAC), the more common forms [6-9].

Due to the absence of different clinical characteristics in rectal SRCC and a lack of awareness among healthcare providers, there is a risk of misdiagnosis, potentially leading to missed opportunities for timely intervention. In this report, we present a case of rectal SRCC with concomitant components of rectal adenoma, highlighting its unique clinical features. Our aim is to increase awareness among clinicians about the potential existence of these kinds of rare cases during clinical prognosis, ensuring that appropriate attention and management are given to them. We adhered to Surgical Case Report Guidelines when preparing this case report.

CASE SUMMARY:

A 29-year-old male with no significant medical history presented to the ER on September 25, 2023, reporting lower abdominal pain and absolute constipation lasting for the past two days. Prior to this episode, the patient had been in good health. The patient presented with severe abdominal pain, multiple episodes of non-bloody vomiting, and an inability to pass flatus or stool for the past two days. Additionally, the patient has been experiencing intermittent episodes of diarrhea and constipation over the last two months, often associated with dietary fiber intake. The patient did not have a documented history of genetic diseases.

Upon examination, the patient appeared active and alert with normal consciousness. Vital signs were recorded as follows: Pulse: 89bpm, Blood Pressure: 110/70mmHg, Temperature: 98°F, Respiratory Rate: 18/minute. Abdominal examination revealed abdominal distension, generalized abdominal tenderness, and resonant percussion notes in all four quadrants. Notably, bowel sounds were absent on auscultation. The remainder of the systemic review did not yield any remarkable findings.

The following complete blood count of the patient was realized from the laboratory tests: White blood cells—6.1×10^9cells/L (normal range: 4–10×10^9cells/L); red blood cell count, 4.04×10^12cells/L (normal range is 4.50–6.50×10^12cells/L); platelet count, 122×10^9cells/L (normal range is 150–4000×10^9cells/L) **(Table 1).**

Table 1: Routine laboratory examinations

CBC	TLC 6.1*10^9/L (4-10*10^9/L)	Hb 12g/dl (13-17 g/dl)	PLT 122*10^9/L (150-400 *10^9/L)
LFTs	S TBilirubin 10umol/L (3.4-17.1 umol/L)	S ALT 19U/L (upto 42 U/L)	S ALP 143U/L (65-306 U/L)
RFTs	S Urea 3.8mmol/L (3.3-5.1 mmol/L)	S Creat 51 umol/L (62-120 umol/L)	
Serum Electrolyte	S Na+ 125mmol/L (135-145mmol/l)	S K+ 3.63mmol/L (3.5-5.1mmol/l)	

cogulation profile	PT 11 control 11 (9-12)	APTT 28 control 28 (23-32)
Blood Group	ABO group AB	Rh-D group positive
D-dimer	>200ng/ml (<200ng/ml)	
Serum Albumin	20g/l (38-54g/l)	

CT scan
29 Aug 2023
findings: multiple dilated fluid filled & fecal loaded small & large gut loops with max caliber of small gut loops measures 5.9mm and large one is 9mm. Transtion point is noted at rectosigmoid junction

6 Sep 2023 CT Abdomen with IV/ oral / stomal/ rectal contrast
Asymterical circumferential thickning of gut involving sigmoid colon & rectum ,RS junction . Sigmoid & desending colon show haustral thickning
lymphnode mesorectum >4 no. , left para arotic , aorto caval, Rt & Lt internal iliac , Rt & Lt inguinal region , CEMRI
TNM — T4bN2bM0 III C

Exploration Laparotomy + loop colostomy 29 Aug 2023
findings: hard nodular fixed rectal mass dilated large bowel with anlarged lymph node in mesentary

diagnosis confirmed by Histopathology
colorectal adenocarcinoma signet cell type

CT scan of chest and abdominal region presented mild PE with AP depth of 13mm and multiple dilated fluid-filled and fecal-loaded loops are observed in both the small and large intestines.

The maximum caliber of the small intestine loops measures 5.9 mm, while the large intestine loops have a maximum caliber of 9 mm. A transition point is identified at the rectosigmoid junction.

The radiological findings strongly suggest the presence of intestinal obstruction, characterized by significant dilation of gut loops and fecal impaction. A distinct narrowing or transition point was evident at the rectosigmoid junction. Following the radiological findings and clinical evaluation, the patient undertook for an exploratory laparotomy, which exposed dilated gut loops within the abdominal cavity, presence of a hard, nodular, and fixed rectal mass and enlarged mesenteric lymph nodes were noticed.

During the procedure, the rectal mass biopsy was taken and sent for histopathological examination, along with immunostaining to further characterize the tissue. To address the condition, a loop colostomy was performed, and a drain was placed in the left pelvic

region. These surgical interventions were carried out to manage the patient's condition and obtain essential diagnostic information for appropriate treatment planning.

Histological examination revealed rectal mucosa infiltrated by malignant neoplasm comprising of sheets and singly scattered atypical cells. Cells have signet cell morphology. Focal mucinous differentiation also seen. One out of two lymph node was involved by malignant neoplasm and above mentioned histology and immunostaining was positive for Cytokeratin **(Figure 3).**

A **B**

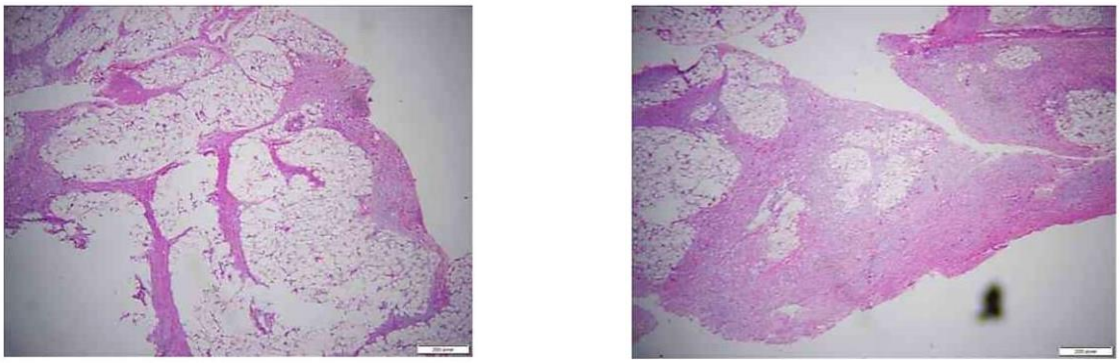

Figure 3: Rectal mucosa infiltrated by malignant neoplasm comprising of sheets and singly scattered atypical cells. Cells have signet cell morphology. focal mucinous differentiation also seen

The staging system employed for this case was the American Joint Committee on Cancer (AJCC) TNM system, which indicates T4bN2bM0.

After successfully addressing the small bowel obstruction through surgical intervention, the patient from the hospital was discharged and scheduled for outpatient oncology follow-up to initiate palliative chemotherapy.
Figure 4 (A, B and C) represents the CT Abdomen with IV/ oral /rectal contrast (after exploratory laparotomy + loop colostomy). Asymmetrical circumferential thickening of gut involving sigmoid colon and rectum, RS junction. Sigmoid and descending colon show haustral thickening lymph node, mesorectum >4 no., left para arotic, aorto caval, Rt and Lt internal iliac, Rt and Lt inguinal region, stoma in left hemiabdomen shows no contrast leak TNM ---- T4bN2bM0 III C.

A **B** **C**

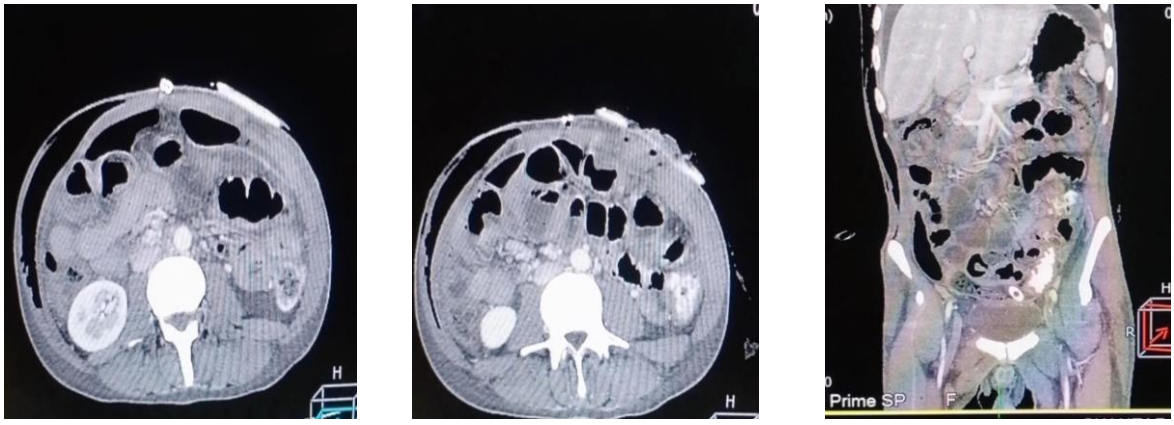

Figure 4: CT Abdomen with IV/ oral /rectal contrast (after Exp laporatomy + loop clostomy)

DISCUSSION:

Laufman and Saphir in 1951 initially describe primary SRCC of colon and rectum remains an infrequent entity [10]. The reported incidence is about 1% [11,12]. Clinical symptoms of colorectal SRCC often resemble those of most CRCs. These symptoms commonly include abdominal pain, hematochezia (the passage of fresh blood through the anus, often in or with stools), a change in bowel habits, altered appetite, and loss of weight. The classic appearance of SRCC of the colorectum in colonoscopy includes a thickened bowel wall, usually more circumferential and diffuse as compared to gland-forming adenocarcinoma. This visual difference can be a valuable indicator for healthcare professionals during the diagnostic process [13]. In 20th century a study conducted [13] revealed that among 12,000 cases of primary colon cancer, only 11 were diagnosed as primary signet-ring cell carcinoma of the colon, resulting in an incidence rate of less than 1 per 1,000 cases of common colorectal adenocarcinoma. Notably, in around 80% of instances [14], these lesions were localized in the left colon, specifically at the distal end of the splenic flexure. This rare variant of colorectal cancer possesses unique clinical, pathological, and biological characteristics that distinguish it from typical colorectal cancer. Importantly, primary signet-ring cell carcinoma can be recognized as an independent prognostic factor associated with unfavorable outcomes in colorectal cancer, regardless of the disease stage [15].

In summary, SRCC is linked to earlier onset, heightened aggressiveness, and a less favorable prognosis [16].

In a study of population conducted in 2020 with a sample size of 3,278, the distribution of primary colorectal SRCC cases was as follows:

1. Most cases were observed in the cecum-transverse colon, accounting for approximately 60.49% of cases.
2. The rectum had the next highest incidence, comprising about 19.52% of cases. The descending colon-sigmoid region accounted for approximately 15.71% of cases.

This distribution pattern indicates that the majority of primary colorectal SRCC cases in the study were located in the cecum-transverse colon, followed by the rectum and the descending colon-sigmoid region [17].

Table 2: Clinicopathological details [18]

Clinicopathological Details	Values
Mean Age (Range) (years)	57.1 (6-79)
Sex (Male/Female)	21 (M) / 5 (F)
Mean Size (Range) (mm)	16.0 (2-45)
Site of Lesions	
Right-Sided Colon (Cecum/Ascending/Transverse)	13 (3/1/9)
Left-Sided Colon (Descending/Sigmoid)	7 (3/4)
Rectum	6
Depth of Invasion	
Intramucosal	6
Submucosal	20
Macroscopic Features	
Polypoid	10
Flat	3
Depressed	13
Lymph Node Metastasis	
Positive	2

A previous study [19] aimed to assess the prognostic significance of different subtypes of histology in various tumor locations and stages of CRC. A comprehensive analysis was conducted using the Surveillance, Epidemiology, and End Results (SEER) database covering the years 1973-2011, which included data from 818, 229 CRC patients with diverse clinical and pathological characteristics. The primary focus was to evaluate the prognostic implications of each histological subtype.

When the analysis was stratified by tumor stage, the findings were as follows:
-SRCC seems to be associated with the worst survival across all the stages of right colon cancer (I: log-r mode, $p = 0.002$; II: log-r mode, $p = 0.03$; III: log-r mode, $p < 0.001$.

-In RC, SRCC was associated with significantly worse survival (log-rank, $p < 0.001$).
-In stages II, III, and IV of left colon cancer, SRCC was also linked to poorer survival (log-rank, $p < 0.001$).

Furthermore, the multivariate survival analysis identified several significant factors associated with worsened survival in CRC, including the SRCC subtype, male gender, age of 70 years or older, tumor size of 5 cm or greater, stage progression, and poor differentiation ($p < 0.001$ for each).

Interestingly, MC emerged as an independent protective factor for the prognosis of right colon cancer ($p = 0.003$), indicating that it was associated with a more favorable outcome in this specific location.

In summary, the study's results suggested that among the three histological subtypes of CRC analyzed, SRCC was associated with the poorest survival. MC, on the other hand, was linked to a better prognosis specifically in right colon cancer but did not demonstrate a similar protective effect in other tumor locations.

Diagnostic colonoscopy with biopsy has traditionally been the primary approach for initial detection of SRCC. Nevertheless, this diagnostic process poses several challenges for a variety of reasons. Firstly, colonoscopy findings can lack specificity, often presenting as thickened bowel walls with fibrosis, diffuse circumferential thickening, or strictures. Superficial ulcerations, similar to those observed in this case, can also be identified and are sometimes mistaken for symptoms of inflammatory bowel disease [20]. This lack of specificity can make accurate diagnosis more difficult.

Secondly, typical pathological features characteristic of SRCC may not be evident in the initial biopsy sample. Initial biopsies of SRCC cases have, in some instances, revealed inflammatory changes similar to granulation tissue and abundant fibrinopurulent exudate [21,22]. This can be further involved in reducing the sensitivity of diagnostic colonoscopy with biopsy. Indeed, there is only one single-centered case series from China, which reported that 25% of lesions were initially misdiagnosed as inflammatory changes and that 31% of cases yielded false-negative results through an endoscopic biopsy [23].

To enhance diagnostic accuracy and facilitate early cancer cell identification, immunohistochemical testing may offer valuable assistance. SRCC has been observed to exhibit positivity for several markers, including estrogen receptors, CDX2, mucin2, Her Par 1, and mucin 5AC. While Her Par 1 is typically associated with gastric origin, SATB homeobox 2 and CDX2 are suggestive of colorectal origin [24-26]. Among the commonly used markers are CK20, CK7, and CDX2. In cases of colorectal origin, it is typical to observe positive CK20 staining and negative CK7 staining [27]. Additionally, a positive SATB staining can indicate a primary tumor in the lower gastrointestinal tract [28].

However, when it comes to identifying colorectal SRCC, the standard immunostaining markers may not be specific enough. SRCC presents a unique immunohistological profile that involves CK20, CDX2, MUC2, and MUC5AC, with variable expression of MUC1 and HepPar1. In colonic SRCC, you would typically see negative HepPar1 staining, consistent CDX2 nuclear positivity, and diffuse cytoplasmic positivity for MUC2 and MUC5AC. This specific staining pattern can be valuable in distinguishing colorectal SRCC from SRCC of gastric origin, which would typically exhibit positive HepPar1 staining and heterogeneous CDX2 staining [29].

However, it's essential to note that the specificity of these markers can still be relatively low. Studies that specifically focus on young patients aged 20-29 years with SRCC of colorectal origin are quite limited in number, with approximately 13 cases reported in the

available literature, including the case being discussed (as outlined in Table 3). The gender distribution among these cases is notable, with a male-to-female ratio of 3:1. Importantly, common diseases that could be associated with young SRCC patients in this age group include a history of inflammatory bowel diseases such as ulcerative colitis and Crohn's disease. In terms of additional clinical characteristics among these young patients:

- A positive family history of colorectal cancer was reported in only 2 out of 12 cases.
- Approximately 2 out of 12 cases had polyps.
- Metastasis was observed in approximately half of the cases, affecting 7 out of 12 patients.
- A significant portion of these young patients, specifically 8 out of the 12, received chemotherapy as part of their treatment regimen.

These findings provide insights into the clinical features and management approaches in this relatively rare subset of young patients with colorectal SRCC.

Given the limited number of cases and the occurrence of SRCC in patients without a history of familial cancers, it may be probable that not yet established risk factors or found to be related in not yet identified risk factors with certain environmental risks of these individuals to be prone to SRCC. Further research and investigation are essential to uncover these potential factors and gain a more comprehensive understanding of SRCC in patient.

Table 3: Cases of SRCC of colorectal origin

No	Citations	Age (years)	Gender	History of IBD	Family History	Polyps	Location	Lymph nodes	Distant metastasis	Chemotherapy
1	Posey et al. [27]	25	M	N/A	N/A	–	R	+	+	+
2	Nakata et al. [40]	22	F	N/A	–	–	DC	–	–	N/A
3	Kilickap et al. [29]	29	M	N/A	N/A	–	R	+	+	+
4	Derici et al. [30]	23	M	-	+	–	R	+	–	–
5	Charles et al. [31]	24	M	N/A	+	–	R	+	+	+
6	Kang et al. [32]	21	M	-	N/A	+	R	–	–	N/A
7	Prabhu et al. [41]	28	F	-	N/A	–	TC	–	–	+
8	Dhull et al. [34]	26	F	N/A	N/A	–	R	–	–	+
9	Turati et al. [35]	29	M	N/A	N/A	–	R	+	+	+
10	Zhou et al. [36]	27	M	N/A	N/A	–	TC	N/A	+	N/A
11	Khan et al. [37]	20	M	N/A	N/A	+	TC	+	+	+
12	Lusilla et al. [39]	25	M	N/A	N/A	–	R	–	+	+

M: male; F: female; IBD: inflammatory bowel disease; CD: Crohn's disease; UC: ulcerative colitis; R: rectum; TC: transverse colon; DC: descending colon; SC: sigmoid colon; AC: ascending colon; C: cecum; N/A: not available

CONCLUSION:

In conclusion, SRCC, a rare histopathologic subtype of CRC, demonstrates distinctive clinical characteristics and an eccentric localization in the colon, warranting a comprehensive diagnostic approach. It is imperative to include SRCC in the differential diagnosis of adolescent and young adult (AYA) patients who present with extended and nonspecific gastrointestinal problems. The SRCC is known for its destructive nature and tends to have a poorer prognosis when diagnosed at an advanced stage. In addition, it is paramount to exclude a possibility of primary malignancy in the gastrointestinal tract that has metastasized to the colon in an atypical way. Further analysis of molecular factors associated with this aggressive subgroup of CRC may assist in the treatment course of action and likely produce better ways of prognosis.

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