



## Signet Ring Cell Carcinoma of the Colon: Exploring the Literature Surrounding this Uncommon Clinical Entity

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### Abstract

Signet ring cell carcinoma of the colon is an uncommon, aggressive variant of colorectal cancer that is typically advanced at presentation. 5-year survival is poor, particularly when compared to adenocarcinoma of the colon. Despite being first reported on in 1951, the amount of clinical research that has been carried out on this entity is limited. Here we report the case of an 88-year-old male who presented with signet ring cell carcinoma of the colon and underwent surgical resection. Our literature review describes the many factors that contribute to the poor prognosis and high recurrence seen in signet ring cell carcinoma of the colon. There is evidence that survival is improved in cases that are recognized early and undergo R0 resection, but clinical guidelines to aid early diagnosis and efficient management are lacking. Evidence-based clinical guidelines on the optimal diagnosis and management of this condition are needed. However, the rarity of this cancer and its propensity for insidious onset and aggressive course prove a challenge to the development of such guidelines.

### Introduction

Less than 1% of colorectal cancers are signet ring cell carcinomas [1-5]. Signet ring cell carcinomas more typically arise in the stomach, with fewer than four percent of cases affecting other organs such as the colon [1,6-8]. Signet ring cell carcinoma is characterized by large mucin-containing vacuoles which displace the cell nucleus to one side, giving them their “signet ring” appearance [1,4]. This aggressive clinical entity was first reported on by Laufman and Saphir in 1951 [1,7].

This cancer is often advanced at presentation and associated with poor prognosis. Due to its rarity, there is scarce clinical evidence to guide early diagnosis and effective management of this clinical entity. In this case report, we describe a case of signet ring cell carcinoma of the colon that was managed with primary surgery.

### Case Report

An 88-year-old gentleman presented to the medical assessment unit with lethargy, malaise and loose bowel motions. The patient denied any rectal bleeding or any other symptoms of note. He was found to be anaemic, with haemoglobin of 8.6. Carcinoembryonic Antigen (CEA) was raised. Our team was consulted at this stage and a colonoscopy was organized. This showed a large lobulated mass at the upper caecum/ascending colon (Figure 1). Multiple biopsies were obtained. Histology revealed a poorly differentiated adenocarcinoma with signet ring cells and 90% mucinous differentiation. A staging CT thorax, abdomen and pelvis (TAP) showed no evidence of metastases.

The case was discussed by the multi-disciplinary panel and primary surgery was recommended. After pre-operative anaesthetic review, the patient underwent right hemicolectomy. The tumour was located adjacent to the ileocecal valve and measured 10 cm in maximum diameter. It had infiltrated through the full thickness of the bowel wall into the mesocolic fat, but the omentum was not involved. R0 resection was carried out with a minimal distance of 90 mm from the tumour to the nearest longitudinal margin (Figure 2). Five of nineteen lymph nodes that were removed showed metastatic disease. There was evidence of lymphovascular space invasion, but no perineural or venous invasion. Final histology confirmed pT4aN2Mo poorly differentiated signet ring adenocarcinoma; Duke’s Stage C.

The patient recovered well post-operatively and was discharged without any significant complications. He did not require any adjuvant treatment. At the time of writing, the patient was disease free.

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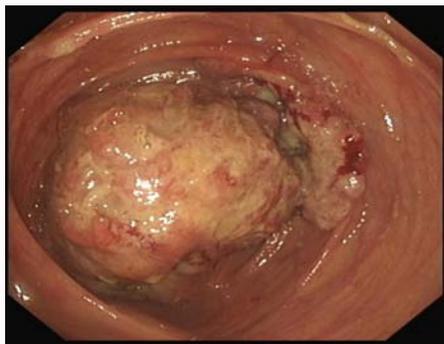
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**Figure 1:** Signet ring cell carcinoma in the upper caecum as visualized at colonoscopy.



**Figure 2:** This specimen was resected surgically.

## Discussion

Signet ring cell carcinoma of the colon is often advanced at presentation, featuring node positive disease and metastatic spread [2,6-8]. Less than 3% are diagnosed at UICC stage I, while more than 87% of cases are stage III or IV at diagnosis which is significantly higher than the 48% of adenocarcinomas diagnosed advanced stages [2,4,5]. The patient described in this case report presented with stage III signet ring cell carcinoma.

Symptoms that are suspicious for colorectal cancer include rectal bleeding (PPV =2.4%), weight loss (PPV =1.2%), abdominal pain (PPV =1.1%), or altered bowel habits (PPV =3%) [1,9-12]. Physical examination may elicit abdominal tenderness or uncover a mass (PPV =1.1%). Digital rectal examination can reveal a mass (PPV =4%) [11,12]. As described in the above case, investigations may reveal iron deficiency anaemia or raised tumour markers, such as CEA [11]. The usefulness of tumour markers in screening for colorectal cancer is low due to their poor sensitivity and specificity, but they do play a role in the evaluation of response to treatment [13,14].

Some patients with colorectal cancer will be asymptomatic and the tumour will be uncovered incidentally [12]. Many patients are picked up through bowel screening programmes. European guidelines advise that all men and women between 50 years -74 years carry out the faecal occult blood test at least every two years [14]. In Ireland, the National Bowel Screening Programme has been implemented for adults between the ages of 60-69. Those with positive results are followed up with further investigation.

The Royal College of Surgeons (RCSI), Ireland, recommends complete examination of the bowel in suspected colorectal cancers. Total colonoscopy or endoscopic visualization of the rectum combined with double contrast barium enema can be used. Where possible, histological confirmation of diagnosis should be obtained

from suspicious lesions prior to surgery [12,14]. In our case, colonoscopy was used to visualize the lesion and obtain a biopsy. Colonoscopy has a sensitivity of 96.1% (CI: 90.4% to 97.2%) in detection of colorectal cancer [15].

Magnifying endoscopy with narrow band imaging is an endoscopic technique that has been successfully used to visualize early signet ring cell carcinoma and remove it via endoscopic resection. The lesion is described as having a dense mucous coating that is difficult to stain with 0.2% indigo-carmin and 0.05% crystal violet to view "pit patterns" [16,17].

Once a tumour has been identified, it is important to investigate what stage it is. CT or Magnetic Resonance Imaging (MRI)-TAP are the imaging modalities of choice for TMN staging. Endoluminal ultrasound can also be used as part of this assessment [12]. Imaging reveals the size of the tumour, the extent of local spread and the presence or absence of distal metastases.

Metastases are commonly found on presentation in signet ring cell carcinoma of the colon; up to 1/3 of patients present with metastatic disease [9]. Signet ring cell carcinoma of the colon metastasizes locally to lymph nodes or the peritoneum [9,12,18]. One study found lymph node metastases in 86% of patient with signet ring cell carcinoma. 41% had peritoneal metastases [4]. The propensity of signet ring cell carcinoma for peritoneal seeding is thought to be linked to the production of significant amounts of mucous under pressure. Another factor that contributes to this is the loss of E-cadherin, which creates cells with greater infiltrative capacity [18]. Distal sites of metastases include the liver or lungs [9,12,18]. 9% of patients have liver metastases [4].

Signet ring tumours are more aggressive than adenocarcinoma of the colon, with poor survival and rapid progression [1,3]. Cause-specific 5-year survival is 21 +/- 8% in signet ring cell carcinoma, as opposed to 67 +/- 1% in adenocarcinoma [2]. The mean survival time was reported to be 45.4 months (95% CI, 26.9 to 63.8 months) in patients with a first presentation of signet ring cell carcinoma and recurrence is 30% more likely than in adenocarcinoma of the colon [2,6,9].

The late presentation of signet ring carcinoma of the colon is a contributing factor to this poor prognosis [4]. It has been hypothesized that the reason for late presentation of signet ring cell carcinoma of the colon is partially due to its intramucosal spread with relative sparing of mucosal surface which leads to fewer symptoms at an early stage [1,8].

One case report that describes a patient with early stage signet ring cell carcinoma of the colon found that the patient had no suspicious signs or symptoms, no family history of colorectal cancer and a normal blood profile, including tumour markers, when a stage IIa 9 mm tumour in the caecum was picked up incidentally at colonoscopy [8]. A trend in the few case reports that describe early signet ring cell carcinoma of the colon is that it tends to be uncovered in an asymptomatic patient with no significant clinical signs or laboratory markers [17]. This poses a significant challenge to the unearthing of this malignancy as no markers have yet been discovered that correlate with the early stages of disease.

Primary curative management of signet ring tumours is surgical resection [1]. There is a mean overall survival post-resection of 33.3 +/- 7.1 months (95% CI, 19.4 to 47.2 months) and a mean progression-

free survival of 11.8 +/- 3.5 months (95% CI, 4.9 to 18.7 months) [4]. Endoscopic mucosal resection is an alternative to surgical resection. It can be useful in the resection of smaller tumours without local invasion [8].

Evidence for the effectiveness of adjuvant chemotherapy in signet ring cell carcinoma of the colon is conflicting [18]. However, some studies show improved survival in patients that receive adjuvant chemotherapy, including a Dutch population-based study of 1,972 individuals with signet ring cell cancer of the colon which reported significantly improved survival in patients with stage III signet ring cell carcinoma of the colon that received adjuvant chemotherapy [5,6]. In this case, the patient did not receive adjuvant chemotherapy.

The role of radiotherapy in the management of signet ring cell carcinoma of the colon is generally limited to palliative therapy.

Certain factors that confer a better prognosis in patients with signet ring cell carcinoma of the colon may provide guidance for optimizing management.

The TMN stage and the grade of the cancer affect survival significantly. Prognosis is better when cancers are picked up at an early stage when there is no lymphovascular/local organ invasion or distal metastases [4,6,17]. 5-year survival for patients with T2 tumours is 75%, while the 5-year survival of T3 tumours is 5.1% and T4 tumours is 0% [19].

Early diagnosis increases the likelihood of successful surgical intervention. Most case reports that describe disease-free survival for more than 5 years are cases that were discovered and treated at an early stage [8,17]. Surgical technique also plays a role in survival. It has been shown that R0 resection confers a better survival than resection with positive margins. Survival is also better in patients that receive elective surgery as opposed to emergency surgical resection. As would be expected, curative surgery confers a better prognosis than palliative surgery [4].

In the case of the patient detailed in this case report, the prognosis is poor due to late presentation with a stage IIIC cancer, which is associated with a 5-year survival of 5.1%. However, the absence of metastatic disease and uncomplicated R0 resection will have a favorable effect on prognosis. At the time of writing, the patient had recovered well post-operatively and was disease free.

## 1

This review of literature highlights the characteristic features of signet ring cell carcinoma of the colon, including its propensity for late presentation with metastatic spread and aggressive course. Most cases that are picked up early are uncovered incidentally in patients with no symptoms, physical signs, or abnormal laboratory results. This suggests that, outside of typical screening regimens for colorectal cancer, there is currently no diagnostic method that shows promise for the early detection of signet ring cell carcinoma of the colon. The development of more sensitive and specific methods of diagnosing signet ring cell carcinoma of the colon at an early stage is needed. This is supported by the fact that many favorable prognostic indicators for survival in this cancer are linked to early detection; including TMN stage and the ability to effectively surgically resect the lesion.

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