Multifocal Intraluminal Gastric and Colonic Recurrence of Anorectal Signet-ring Cell Carcinoma: A Case Report

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ABSTRACT

Extra-anastomotic intraluminal recurrence of colorectal cancer (CRC) is uncommon. A 44-year-old female underwent abdominoperineal resection for non-metastatic, stenosing anorectal cancer. Histopathology showed a T4aN2b poorly-differentiated signet-ring cell carcinoma. Postoperative chemoradiotherapy was completed. Twelve months post-surgery, serum carcinoembryonic antigen (CEA) level was elevated, with colonoscopy showing a right-sided malignant lesion on biopsy. Right colectomy was performed, with extensive tumour deposits found on the resected specimen. Morphological features, immunoprofile and molecular profile of the tumours were consistent with metastases from the previous anorectal primary. Gastroscopy also revealed multifocal small gastric polyps with identical signet-ring cell features. Palliative chemotherapy was commenced, with the patient eventually succumbing to the disease. Reported here is the first known case of multifocal intraluminal recurrence in the right colon and stomach from an anorectal cancer, likely from implantation metastases. Further studies are warranted to shed light on the mechanisms involved in this rare form of CRC metastasis.

Key words: Colorectal cancer, multifocal intraluminal metastases, colorectal cancer recurrence

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Multifocal colorectal cancer (CRC) is diagnosed in approximately 5% of all CRC patients, presenting in either a synchronous or metachronous fashion. In general, the most important risk factors for the development of multifocal CRC are inflammatory bowel disease or an underlying genetic predisposition, including hereditary colorectal cancer syndromes.

The presence of exfoliated tumour cells within the bowel lumen has also led to the recognition of intraluminal cancer seeding and implantation.[1-3] This phenomenon often results in recurrence of CRC at areas of bowel injury or trauma, including the bowel anastomosis[4], colostomy site[5-6], or inflammed areas.[7] Nonetheless, intraluminal CRC recurrence has also been reported in normal small bowel.[8-12]

The distinction between a metachronous primary tumour and recurrence can be challenging. In 2021, the Dutch Multifocal Colorectal Cancer Study Group analyzed the tumour DNA of 24 patients with multifocal CRC, who were initially thought to have multiple independent CRCs. One-third of these patients were found to have clonally related CRC based on mutation, DNA copy number, or both. As germline mutations and inflammatory bowel disease were excluded, intraluminal tumour seeding was hypothesized as a likely explanation.[13]

The authors describe a case of multifocal intraluminal recurrences to the right colon and stomach from a prior anorectal cancer. To our knowledge, this is the first such case reported in literature.

THE CASE

A 44-year-old Chinese lady presented with change in bowel habits and intermittent lower gastrointestinal obstructive symptoms associated with 10% weight loss over 1 month. She had no prior medical history and no family history of malignancy or hereditary cancer syndromes. Examination and flexible sigmoidoscopy revealed a circumferential stenosing anorectal tumour 4 cm from the anal verge involving the puborectalis muscle. The tumour was traversable via endoscopy and there were no other colonic lesions seen at the time of initial colonoscopy. Histology showed a poorly differentiated signet-ring cell mucinous adenocarcinoma. Initial serum carcinoembryonic antigen (CEA) was normal at 2.9 ug/L. Computed tomography (CT) of the chest, abdomen and pelvis demonstrated no distant metastasis nor other tumours. Magnetic resonance imaging of the rectum confirmed a clinical stage cT2N0 anorectal tumour with uninvolved circumferential resection margin (CRM). The case was discussed at the multidisciplinary tumour board (MDT) and planned for upfront surgery, given the tumour was deemed resectable (cT2N0) and there were no obvious nodal or distant metastases seen on imaging.

The patient underwent laparoscopic abdominoperineal resection with an uncomplicated postoperative recovery. Operative specimen images are shown in Figure 1. Histopathology revealed a pT4aN2b (7 out of 19 lymph nodes) poorly differentiated signet-ring cell carcinoma (Figure 2). All resection margins were clear. Perineural and lymphovascular invasion were present. In-house multiplex polymerase chain reaction (PCR) assay screen for gene alterations in mutational hotspots and targeted regions in genes implicated in colon cancer showed no variants detected in KRAS, NRAS and BRAF. There was normal expression of mismatch repair proteins. Overall findings were consistent with a stage IIIC anorectal adenocarcinoma. She initially underwent 6 cycles of adjuvant oxaliplatin with capecitabine (XELOX). Surveillance CT scan at postoperative 6 months did not demonstrate evidence of disease recurrence. Thereafter, she completed an additional 6 cycles of capecitabine with pelvic radiotherapy (45Gy/25# + 5.4Gy/3#). Serum CEA remained normal.

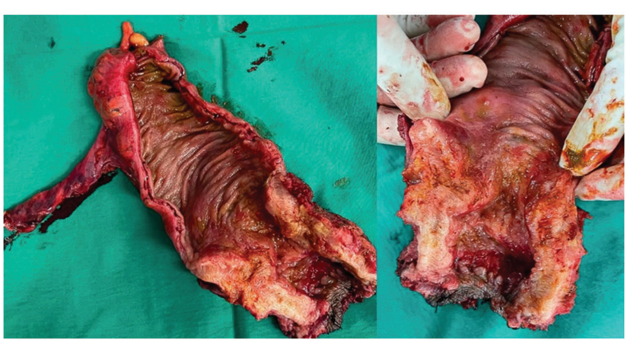

Figure 1. Abdominoperineal resection specimen.

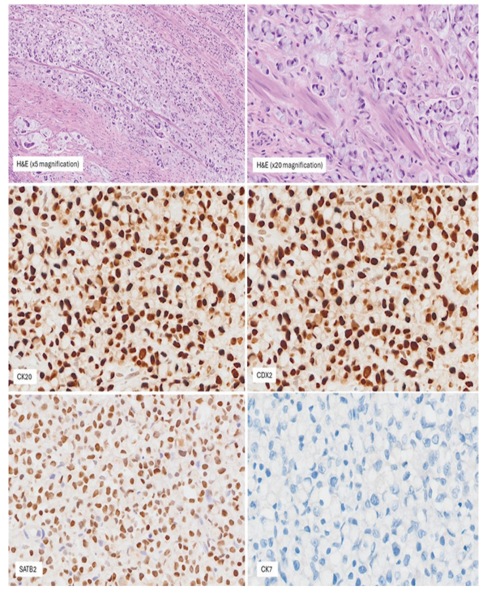

Figure 2. Signet-ring cell carcinoma on histology.

Twelve months post-surgery, the CEA was found to be elevated at 8.0 ug/L as compared to normal previously. CT of the chest, abdomen and pelvis showed no evidence of local recurrence, lymphadenopathy nor distant metastases. However, colonoscopic assessment showed two caecal polyps (2 mm each) and two ascending colon polyps (3 mm and 4 mm) (Figure 3). Polypectomy was performed and histological examination of all four polyps revealed poorly differentiated adenocarcinoma with signet-ring cell features, consistent with metastases. A PET-CT scan was performed which did not show any FDG-avid lesions. Her case was rediscussed at the MDT, and consensus was to proceed with surgical resection.

Figure 3. Right colonic lesions seen on colonoscopy 12 months post abdominoperineal resection.

She underwent a right hemicolectomy approximately one month following colonoscopy. No extra-colonic lesions were seen intraoperatively. The cut specimen showed several other small polyps (Figure 4). Gross margins were free of lesions. Postoperative recovery was uneventful. The histopathological examination of the right hemicolectomy specimen revealed 14 polyps (ranging from 3 to 10 mm in size) and extensive microscopic tumour deposits with lymphovascular invasion throughout the resected bowel (including the appendix) in the submucosa, muscularis and subserosal layers, as well as at the mesenteric and distal margins, all of which were signet-ring cell carcinoma. 20 out of 20 resected lymph nodes were positive for carcinoma. Morphological features, immunoprofile and molecular profile of the tumours were consistent with metastases from the previous anorectal primary.

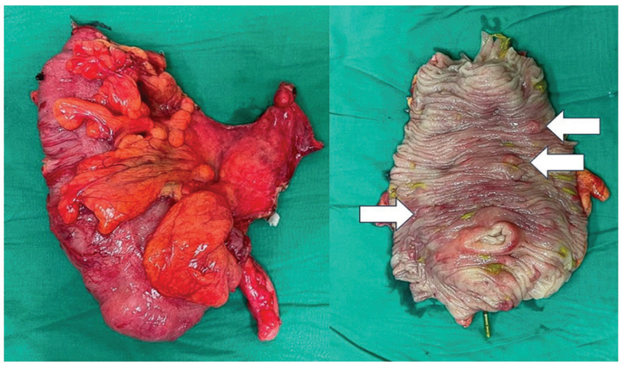

Figure 4. Right hemicolectomy specimen showing several mucosal lesions.

Given her unique presentation with extensive intraluminal recurrence, a decision was made to repeat the CEA postoperatively to monitor its trend post-resection. On follow-up two weeks after surgery, the serum CEA had increased from 8.0 to 58.2 ug/L despite the surgical resection. In view of the persistently raised CEA level, despite resection of the colonic recurrence, gastroscopy was performed which showed multiple gastric polyps throughout the stomach, ranging from 5 to 10 mm in size (Figure 5). Biopsies of these lesions showed the presence of signet-ring cell carcinoma with identical features as before. The visualized first and second part of the duodenum were normal.

Palliative chemotherapy was commenced with folinic acid, 5-fluorouracil, oxaliplatin and irinotecan (FOLFOXIRI), with the patient undergoing four cycles in total. Genetic testing showed no pathogenic variant in 56 genes tested (colorectal cancer panel and common cancer panel). Three months later, the patient suffered a stroke secondary to the prothrombotic state from the underlying metastatic cancer. Her condition deteriorated, and she was transferred to inpatient hospice care, succumbing to the disease 18 months from the time of the initial surgery. The final CT scans done one month prior to demise showed new peritoneal metastases, without evidence of hepatic or pulmonary lesions.

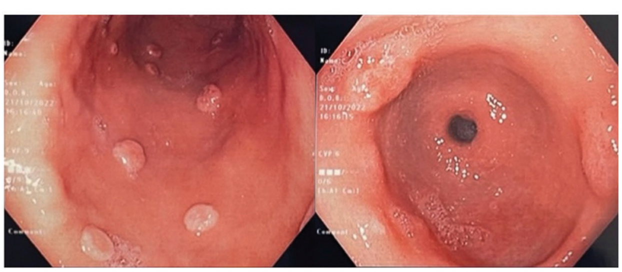

Figure 5. Gastroscopy showing multifocal gastric mucosal lesions.

The patient provided written informed consent for publication of this case report with accompanying images. Ethical approval was not required by our institution for publication of case reports.

DISCUSSION

The three classic routes of CRC metastasis are haematogenous, lymphatic and transcoelomic/transperitoneal, with the most common sites of spread in the lung, liver, pleura/mediastinum and peritoneum.[14] Despite improvements in screening, cancer therapies and surgical techniques, metastasis continues to be one of the major contributors to CRC morbidity and mortality.[15] Paget's "seed-and-soil" analogy of tumour cells seeding within the "soil" of specific tissue microenvironments is commonly used to explain the pathogenesis of metastatic spread.[16]

Riihimäki et al. analyzed more than 49,000 CRC patients using the nationwide Swedish Cancer Registry.[14] Colon and rectal cancers were found to exhibit different patterns of metastasis, with signet-ring cell carcinomas more often metastasizing to the peritoneum and less frequently to the liver. "Other gastro-intestinal" metastases represented 9.3 % and 6.5 % of all colon and rectal metastases respectively, although the exact anatomical locations of the gastrointestinal lesions were not specified.[14]

Intraluminal extra-anastomotic CRC recurrence to proximal bowel following primary tumour resection is uncommon. Several authors have reported metastases occurring at sites of colonic mucosal injury[5-7], yet others arose from seemingly normal bowel.[8-12] These observations demonstrate the probability of exfoliated tumour cell implantation within the bowel lumen. Two cases occurred following initially obstructive CRC[10-11], potentially contributing to retrograde cancer cell reflux and seeding. Moreover, colonoscopy and biopsy of the primary tumour has also been shown to potentially seed cancer cells to other locations in the large bowel.[17]

To our knowledge, this is the first case demonstrating multifocal right colonic and gastric metastases following resection of poorly differentiated signet-ring cell anorectal carcinoma. Genetic predisposition and inflammatory bowel disease were excluded, and the bowel was otherwise healthy, albeit presenting with partial obstruction from the stenosing tumour. In the absence of additional metastases to more conventional sites e.g. lung or liver, intraluminal implantation was postulated to more likely than seeding via the vascular or lymphatic routes. While tumour deposits were detected at the resected terminal ileum (as part of the right hemicolectomy procedure), there was no further evidence of disease over the remaining small intestine. However, no dedicated imaging or endoscopy had been performed for evaluation of the small bowel as palliative management intent had already been established at that time.

While an unknown germline mutation was another possibility, to our knowledge no genetic condition has been described to present in a similar fashion with multifocal colonic and gastric tumours. Moreover, the timing of re-presentation of disease 12 months after surgery with concurrent elevation in CEA, along with the identical histopathological features and immunoprofile of the initial and recurrent tumours suggest disease recurrence instead of new metachronous malignant lesions.

CONCLUSION

Intraluminal extra-anastomotic recurrence is an uncommon form of CRC relapse. We report the first known case of multifocal intraluminal recurrence in the right colon and stomach from an anorectal cancer, likely from implantation metastases. Further studies are warranted to shed light on the mechanisms involved in this rare form of CRC metastasis.

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Citation

Chee MYM, Lin W, Ong SYK, Chiang J, Thane NN and Seow-En I. Multifocal intraluminal gastric and colonic recurrence of anorectal signet-ring cell carcinoma: A case report. Arch Colorect Dis 2025; 1 (1): 43-46.