



# Metastatic Gastric Signet Ring Cell Adenocarcinoma Presenting as a Colonic Mass: Case Report of Uncommon Presentation and Review of the Literature

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## Abstract

Gastric cancer (GC) is one of the most common cancers by incidence and number of deaths. Gastric cancer is more prevalent in males with the strongest risk factor being Helicobacter pylori infection. Signet ring cell adenocarcinoma (SRCA) is a subtype of GC associated with a worse prognosis due to late presentation. SRCA is more likely to be metastatic at presentation compared with other subtypes of GC. We present a case of metastatic gastric SRCA presenting as a colonic mass with associated ascites and pleural effusion. This case highlights the importance of including metastatic gastric SRCA in the differential diagnosis in patients presenting with gastric and colonic dual SRCA. It is vital to determine if it is a metastatic tumor or two primaries as this would change staging and treatment protocols.

**Keywords:** Gastric cancer; Signet ring cell carcinoma; Metastasis, primary

## ABBREVIATIONS

**GC:** Gastric cancer, **SRC:** Signet ring cell, **SRCA:** Signet ring cell adenocarcinoma, **IHC:** Immunohistochemistry

## INTRODUCTION

Gastric cancer (GC) is a major public health concern with incidence of over one million in 2020. GC is the third leading cause of cancer related death in the world [1]. While the incidence of GC has decreased over the years, the incidence of signet ring cell adenocarcinoma (SRCA) subtype of GC has steadily increased [2]. About 16% of all GC are classified as SRCA. Compared to other GC, SRCA has an earlier age of presentation, more likely to be metastatic than primary (43.0% vs. 37.3%) and have a higher grade histomorphology (75.4% vs. 52.1%). SRCA is associated with a worse prognosis due to larger tumor size, diffuse stomach involvement and advanced stage when compared to other types of GC. Survival rates of SRCA are lower at all time points; 5-year (19.2% vs. 25.8%) and 10-year (16.0% vs. 22.1%) [3]. Histologically, SRCA is characterised by poorly cohesive malignant cells with intracytoplasmic mucin encompassing more than 50% of the tumor [4]. Linitis Plastica is the macroscopic

presentation of a diffuse infiltrating carcinoma of a hollow organ, usually the stomach, causing it to retain its shape but remain stiff and contracted. SRCA, a clear example of Linitis Plastica, is an aggressive carcinoma with the most common metastatic site being the regional lymph nodes [5]. There have been very few cases of gastric SRC with metastasis to the colon [1].

We present a case initially presented as ascites, pleural effusion, and colonic mass. Although no stomach mass was identified, and only thickening of the gastric wall was noted, pathology investigation traced the primary malignant lesion to the stomach. Final diagnosis was metastatic SRCA arising from the stomach with metastasis to the colon and spreading into the peritoneal cavity and pleural space.

## CASE PRESENTATION

A 68-year-old man presented with acute marked abdominal distension and difficulty breathing with exertion. He complained of recent weight loss, lethargy, and malaise as well as occasional episodes of hematemesis. On imaging, ascites and bilateral pleural effusion were observed. In addition, imaging showed a large 6.5 x 3.5 cm infiltrating flat mass located in the right colon 7 cm distal to the appendix. Radiographic findings were suggestive of colonic carcinoma with recommendation for tissue diagnosis.

His medical history was significant for obesity, controlled type-II diabetes, and controlled hypertension. He had been consuming up to 8 glasses of wine every day for many years and quit a few months prior to his presentation. He never used any over-the-counter medications or herbal medications and had no family history of gastrointestinal cancer.

Peritoneal fluid and pleural fluid were aspirated for cytopathologic microscopic examination. Cytomorphology showed malignant cells with signet-ring features admixed with malignant glandular cells consistent with metastatic adenocarcinoma. Immunohistochemistry studies performed

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on cellblock preparation showed the malignant signet-ring cells positive for Moc-31, Ber-Ep4, CEA (p), CK7, and CAM 5.2, while negative for CK20 and CDX2. The cytomorphology and immunohistochemistry (IHC) profile were consistent with metastatic signet-ring type adenocarcinoma. The studies were consistent with metastatic tumor from a stomach and not a colon primary. Stomach imaging studies showed no gastric mass but diffuse thickening of the stomach wall more prominent along the body and antrum. Biopsy obtained from the stomach wall showed infiltrating signet-ring adenocarcinoma with identical features to the malignant cells obtained from the peritoneal and pleural fluid. A biopsy sample from the colon mass produced the same diagnosis given to the gastric mass and ruled out a colon primary.

A tumor board multidisciplinary meeting determined the best course of action was to treat with chemotherapy and debulking resection of the colonic tumor to relieve intestinal obstruction in an attempt to improve quality of life

Surgical excision included terminal ileum, right colon and segment of transverse colon. The colonic tumor presented as a flat mucosal area without mucosal folds measuring 6.5 x 3.5 cm. Pathologic microscopic examination showed the tumor to be seen in the serosa, muscularis propria and submucosa and not in the mucosa consistent with metastatic rather than primary tumor (**Figure 1A**). In addition, there was no evidence of in situ carcinoma, which was in support of metastasis. 18 out of 20 dissected pericolic lymph nodes were positive for metastatic adenocarcinoma with signet cell features (**Figure 1B**). The colonic mass showed metastatic signet-ring adenocarcinoma in form of poorly cohesive mixture of signet and non-signet ring cells. IHC studies on the colonic tumor showed the tumor cells positive for CK7 and Cam5.2, while negative for CK20, CDX2, Vimentin, HMB45, LCA and CD30 and positive staining with Mucicarmine (**Figure 1C**) in support of metastasis from gastric primary.

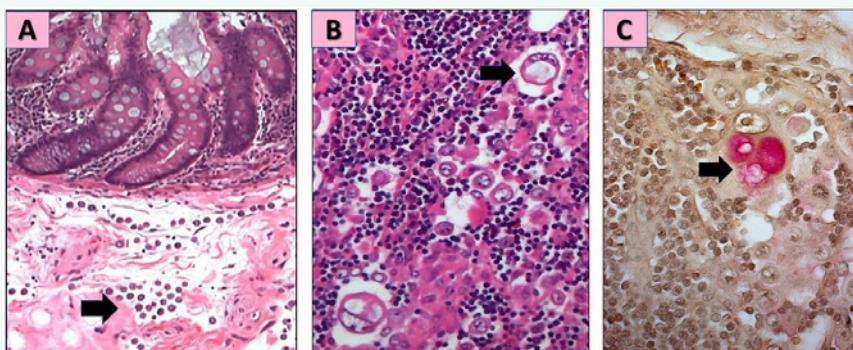
Patient showed mild response to chemotherapy but expired 6 months following the surgery as a result of widespread metastasis and multiple organ failure.

## DISCUSSION

Gastric carcinoma is one of the most common cancers with an incidence of over one million in 2020 [1]. The mean age of diagnosis for GC is around 60 years with an average 5-year survival of 31% in the United States. The strongest risk factor for the development of GC is infection with *H. pylori*. Several non-infectious risk factors that have been identified include genetics, diet, gastric ulcers, gastroesophageal reflux disease, smoking and alcohol use [6]. Males are twice as likely to be diagnosed with GC compared to women [7].

GC most commonly presents asymptotically with up to 50% of patients presenting with non-specific gastrointestinal symptoms such as dyspepsia [8]. GC is only found in 1-2% of patients with dyspepsia who undergo endoscopic evaluation. The absence of early symptoms delays the diagnosis of GC with 80-90% of patients presenting after the cancer has locally invaded or metastasized leading to late diagnosis and lower rates of successful surgical resections. Most patients in the late stage of GC present with vague abdominal pain, anorexia and weight loss. In addition, fullness or early satiety may be present with bulky tumors whereas ulcerated tumors may bleed and present as hematemesis or melena. Advanced GC may present with palpable abdominal mass, bowel obstruction or ascites. GC can metastasize to the ovaries (Krukenberg tumor), left supraclavicular lymph node, left axillary lymph node or perumbilical lymph node [8]. GC symptoms may mimic those of gastric ulcer, gastroesophageal reflux disease, ménétrier disease, nonulcer dyspepsia and other cancers such as MALT lymphoma, sarcoma, neuroendocrine tumor thus rendering diagnosis difficult [5]. Screening for GC is performed in high risk individuals via endoscopy [8]. Diagnosis of GC can be made by biphasic upper gastrointestinal examination using barium or an endoscopy with biopsy. A CT scan is used to stage the patients as it can detect metastasis to regional lymph nodes [9].

Histologically, GC can be categorized by Lauren's criteria or the WHO classification. Lauren's criteria histologically define two subtypes of GC; intestinal or diffuse. The relative incidence



**Figure 1** Microscopic description of the Excised colon mass and lymph nodes

Figure A: Tumor cells scattered through the submucosa (arrow). Mucosa is free of tumor cells  
 H&E stain X20

Figure B: Pericolic lymph node showing metastatic signet ring adenocarcinoma (arrow) (H&E stain X40)

Figure C: Signet ring cells positive for Mucicarmine stain (arrow)

is 54% for intestinal type and 32% for the diffuse type. The diffuse subtype is more commonly seen in young females while the intestinal type is associated with *H. pylori* infection [10]. The various subtypes of GC according to the WHO classification include tubular, papillary, mucinous, poorly cohesive (including SRCA) and mixed carcinomas [11]. The most common subtype is tubular adenocarcinoma. Grossly it forms a fungating mass and histologically it is characterised by irregularly distended, fused or branching tubules of various sizes. The papillary adenocarcinoma tends to affect older individuals and is characterized by epithelial projections with a central fibrovascular core. Mucinous adenocarcinoma is histologically characterised by extracellular mucinous pools constituting at least 50% of tumor volume. Lastly, SRCA is composed of a poorly cohesive mixture of signet and non-signet ring cells. SRCA grossly has extensive desmoplasia in the gastric wall. They most commonly metastasize to regional lymph nodes. Further, signet ring cells (SRC) can have serosal involvement and may even invade the duodenum thus requiring additional scrutiny during surgical resection. Additionally, staining with cytokeratin utilizing intraoperative frozen section can aid in identifying occult SRC in the lamina propria [12]. Immunohistochemistry of gastric SRC has increased prevalence of CK7+/CK20- and CK7+/CK19- patterns. In addition, increased prevalence of metastasis and progression has been observed with the up-regulation of MUC1 and the down-regulation of MUC2, MUC5AC and MUC6 [13].

The Cancer Genome Atlas research network proposed four molecular classifications for gastric adenocarcinomas: positive for Epstein-Barr virus (9%), microsatellite unstable tumors (22%), gnomically stable tumors (20%), and chromosomally unstable tumors (50%). These molecular classifications can be used to determine prognosis and provide targeted therapy. The best studied subtypes include chromosomally unstable and microsatellite unstable tumors. Chromosomally unstable subtype is associated with a poor prognosis due to mutations in various proto-oncogenes and tumour-suppressor genes. However, it is responsive to cisplatin-based chemotherapy. Microsatellite unstable tumors is caused by inherited mutation of mismatch repair gene as part of hereditary non-polyposis colorectal cancer syndrome or by sporadic hypermethylation in the MLH1 promoter region [14]. SRCA is a poorly cohesive subtype of GC associated with early mutations in the E-cadherin gene [15]. Whole genome sequencing of SRCA revealed six significantly associated mutated genes: TP53 (25%), CDH1 (15.6%), PIK3CA (12.5%), ERBB2 (6.3%), LCE1F (6.3%), and OR8J1 (6.3%) [16]. In our case, no molecular studies were performed because it was a late stage and due to insurance reimbursement issues.

Treatment for GC includes chemotherapy, radiation and targeted immunotherapy however the most effective treatment is surgical resection, which may be curative in occasional cases. The 5-year survival of a curative resection was found to be 51.2%. However, most detected GC cases are in stage III or IV. Surgical resection of the GC and the neighbouring metastatic organs have a 5-year survival of 28.3%. In cases where complete surgical resection is not possible, partial tumor resection is not recommended as it does not prolong survival. However, palliative

resection such as removal of an obstruction can be performed to improve quality of life [17].

Previous case reports indicate metastatic spread of GC to the colon is exclusively of the SRC subtype or poorly differentiated subtypes. The three identified routes of metastasis included gastrointestinal lumen, hematogenous and lymphatic with the most common being through the gastrointestinal lumen [18]. The incidence of primary SRC or poorly differentiated type of adenocarcinoma originating from the colon is relatively rare at 6.7% [19]. Thus, gastric SRC with metastasis to the colon should be included in the differential diagnosis of patients presenting with gastric and colon dual SRC.

We bring this case forward to shed light on the importance of including metastatic stomach signet ring cell adenocarcinoma in the differential diagnosis of a patients presenting as a colonic mass with ascites and pleural effusion. It is our hope that this report raises awareness of including this differential, and continued investigation drives further development of efficacious diagnosis and safe treatments for improving patient outcomes.

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