Signet Ring Cell Carcinomas in the Esophagus, Stomach, Duodenum, Ileocecum and Colorectum

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Keywords:
Multiple primary carcinomas; Signet ring cell carcinoma; Esophagus; Stomach; Duodenum; Ileocecum; Colorectum; Case report

1. Abstract
1.1. Background: Multiple primary carcinomas (MPCs), first reported by Billroth in 1879, are defined as two or more synchronous or metachronous cancers unrelated to each other in the same individual. MPCs are rare, especially synchronous signet ring cell carcinomas (SRCCs) of the digestive tract. In this report, we present a rare case of a male patient with synchronous SRCCs in the esophagus, stomach, duodenum, ileocecum and colorectum.
1.2. Case Presentation: A 64-year-old man with a medical history of diabetes mellitus presented with symptoms of abdominal distension, diarrhea and back pain, accompanied by significant weight loss. Physical examination of the patient revealed no abnormal findings and there was no specific family history. Gastrointestinal endoscopy revealed multiple protruding lesions with central depression and erosion in the esophagus, stomach, duodenum, ileocecum, and colorectum, and biopsy of the lesions indicated SRCC. Immunohistochemical staining showed a negative result for cytokeratin 7 (CK7) and a positive result for cytokeratin 20 (CK20) and mucin 2 (MUC2). Due to the wide range of lesions, systemic chemotherapy was given in this case. The patient eventually died five months after the discharge.
1.3. Conclusion: It is difficult to distinguish MPCs from metastatic tumors. The combination of histological morphological evaluation and molecular pathology can assist in the identification of MPCs and metastatic tumors. Accurate diagnosis and treatment have been shown to improve prognosis.

2. Introduction
MPCs refer to two or more independent primary malignancies occurred in the same individual simultaneously or successively, which may occur in different parts of the same organ or in different organs [1]. According to the timing of diagnosis for each constituent tumor, MPCs are classified into synchronous MPCs (within 6 months) and metachronous MPCs (more than 6 months) [1].

In recent years, patients are more frequently diagnosed with MPCs due to better medical technology and comprehensive clinical diagnosis and treatment, but multiple SRCCs of the digestive tract are still extremely rare. Here, we reported a 64-year-old male patient with synchronous SRCCs in the esophagus, stomach, duodenum, ileocecum and colorectum, and hope to raise appreciation for the possibility of such rarer cases during clinical diagnosis.

3. Case Presentation
A 64-year-old man with a medical history of diabetes mellitus presented with symptoms of abdominal distension, diarrhea and back pain, and lost ten kilograms in weight within one month. Physical examination of the patient revealed no abnormal findings and there was no specific family history. Routine hematological examination and biochemical tests were within normal limits. Fecal occult blood test was positive. Tumor markers showed carbohydrate antigen 19-9 (CA199) was 582.49 u/ml (normal range, 0-35u/ml), carbohydrate antigen 12-5 (CA125) was 47.72 u/ml (normal range, 0-35u/ml), carbohydrate antigen 24-2 (CA242) was higher than 500 u/ml (normal range, 0-20u/ml) and keratin 19 fragment
was 7.27 ng/ml (normal range, 0-5u/ml), and alpha-fetoprotein (AFP) and carcinoembryonic antigen (CEA) were normal. On April 21, 2022, the patient underwent gastrointestinal endoscopy in our hospital, which revealed multiple protruding lesions with central depression and erosion in the esophagus, stomach, duodenum, ileocecum, and colorectum (Figure 1), and biopsy of the lesions indicated SRCC (Figure 2). Immunohistochemical staining showed MLH1(+), MSH2(+), MSH6(+), PMS2(+), CK7(-), CK20(+), CDX2(+), β-catenin (cytoplasm +), MUC2(+), MUC6(-) (Figure 3). The specimens of esophagus, stomach, duodenum, ileocecum, and colorectum shared the same manifestation in both microscopy and immunohistochemical staining. Abdominal computed tomography (CT) scan with intravenous contrast was also performed, which revealed uneven thickening of the antral wall with enhancement, consistent with the signs of gastric cancer, and there was also swelling of the retroperitoneal and mesenteric lymph nodes (Figure 4). The patient had a wide range of lesions, esophagus, stomach, duodenum, ileocecum and large intestine are all involved, and developed retroperitoneal lymph node metastasis. Thus, the patient had lost the opportunity of surgery and received systemic chemotherapy. Systemic chemotherapy appears to be effective in SRCC patients, although the observed survival benefit is not as robust as that observed in not-otherwise-specified adenocarcinoma (NOS) patients. Oxaliplatin and Capecitabine combined with Sintilimab chemotherapy were given by our medical oncology department in May of 2022. Unfortunately, the patient eventually died five months after discharge from our hospital.

Figure 1: Gastroenteroscopic findings. Multiple protruding lesions in the esophagus (a), stomach (b), duodenum (c), ileocecum (d) and colorectum (e), with depression and erosion at the top.
Figure 2: H&E staining findings (400×). Specimens of the esophageal (a), gastric (b), duodenal (c), ileocecal (d) and colorectal (e) lesions; showing SRCs with eccentrically placed crescent-shaped nuclei. H&E, hematoxylin and eosin; SRCs, signet ring cells.

Figure 3: IHC staining findings (400×). Gastric (a) and colonic (b) SRCs stained negative for CK7; gastric (c) and colonic (d) SRCs stained positive for CK20; gastric (e) and colonic (f) SRCs stained positive for MUC2. IHC, immunohistochemistry; CK7, cytokeratin 7; CK20, cytokeratin 20; MUC2, mucin 2.
Figure 4: Abdominal CT findings. CT of abdomen showed an uneven thickening of the antral wall with enhancement, consistent with the signs of gastric cancer. There was also swelling of the retroperitoneal and mesenteric lymph nodes.

4. Discussion

SRCC is a poorly cohesive carcinoma composed predominantly of tumor cells with prominent cytoplasmic mucin and a crescent-shaped, eccentrically located nucleus [2]. SRCC is considered to be one of the most aggressive forms of carcinoma associated with invasive biological behavior, a younger age at presentation, higher local lymphatic spread, and peritoneal metastasis [3]. SRCC can primarily be found in the stomach, only a small percentage of approximately 4% having other locations [4]. Clinically, gastric SRCC presents with a high incidence of peritoneal metastasis and lymphatic invasion at diagnosis, while colorectal SRCC most commonly metastasizes to the liver and peritoneum [5, 6]. However, tumor metastasis between the digestive tract is rare. The common sites of intestinal metastasis of gastric cancer are ascending colon and rectum, less involving the small intestine. Gastric metastasis of colorectal cancer is extremely rare. The mechanism of this special metastatic type may be related to hematogenous and lymphatic spread. Typical endoscopic features of metastasis include solitary lesions and submucosal tumors [7].

This is a rare case of synchronous SRCCs in the esophagus, stomach, duodenum, ileocecum and colorectum. It is important to distinguish MPCs from metastatic cancers for better diagnosis and treatment. In this case, the esophagus, stomach, duodenum, ileocecum and large intestine are independent growing cancer foci, and they are mainly mucosal polyp eminence lesions, so they are more likely to be MPCs. MPCs refer to two or more primary malignant tumors occurred in the same individual at the same time or successively. The diagnostic criteria for MPCs proposed by Warren and Gales in 1932 are that each tumor must be malignant, each tumor must have its own unique cellular morphological characteristic, and the possibility that one was a metastatic lesion from another must be excluded [8]. But on the other hand, all the specimens in this case showed the same manifestation in both microscopy and immunohistochemical staining, which showed a negative result for CK7 and a positive result for CK20 and MUC2. Some studies have shown that colorectal SRCC most commonly demonstrated a CK7(-) / CK20(+) staining pattern compared with the predominant CK7(+) / CK20(-) pattern in gastric SRCC [9]. Therefore, it was reasonable to hold the suspicion that the lesions of esophagus, stomach, duodenum and ileocecum were a special pattern of metastasis from the primary colorectal SRCC in our case. Actually, it is difficult to distinguish MPCs from metastatic tumors in some situations. Thus, further molecular studies may be required to assess the clonal relationship for differentiating between the MPCs and metastasis in several cancers. If these tumors demonstrate distinct genomic profiles, all tumors are independent primary tumors, otherwise, they are more likely to be metastasis [10]. Unfortunately, our patient was unable to undergo genetic testing, which can evaluate the clonal relatedness of distinct tumors to determine whether the tumors arise from a common ancestral cell or if they developed entirely independently.

In conclusion, we report a rare case of simultaneous multiple primary SRCCs of the digestive tract. There have been an increasing number of multiple gastrointestinal tumors in recent years. There are significant differences in treatment principles and prognosis between MPCs and metastatic cancers. Metastatic cancers are usually associated with poor prognosis and also affect the treatment, while MPCs should take radical therapy as far as possible with better prognosis. Hence, in clinical work, comprehensive examinations should be performed to improve the detection rate of MPCs. We should pay attention to distinguish MPCs from metastatic cancers, which will be beneficial to guide accurate diagnosis and treatment and improve patients’ prognosis.

5. Author Contributions

Hui Zhou wrote the paper; Jiamei Ma and Yening Xiao made the endoscopic diagnoses; Hong Li made the pathologic diagnoses; Xiaoxi Huang and Zhengyi Chen reviewed the manuscript for important intellectual content; all authors have read and approved the final manuscript.

6. Conflicts of Interest

The authors declare that they have no conflicts of interest.
7. Funding

This work was supported by the Scientific Research projects in Health Industry of Hainan Health Department (20A200456 and 22A200319) and Natural Science Foundation of Hainan Province (823RC603).

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