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Case Report

Synchronous triple primary adenocarcinoma of gastric and transverse colon: a case report

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Abstract: Adenocarcinoma of gastric and colon are common malignancies, while multiple primary cancers in both gastric and colon are rare and easily misdiagnosed. Multiple primary cancers (MPC) are two or more malignancies in an individual without any relationship between the lesions at the same time or successively. The present study reports the rare case of a patient with synchronous triple primary cancers of gastric and transverse colon that received a systematic treatment, including surgical intervention and chemotherapy. The histological examination proved one moderate differentiated gastric adenocarcinoma ($pT1_bN0M0$), one mucinous adenocarcinoma of the transverse colon (pT3N0M0), and another moderate differentiated adenocarcinoma of the transverse colon (pT3N0M0). Finally, we discussed the diagnostic criteria, the risk factors, the treatment criteria and the prognosis of these rare MPC. Although increasing cases of MPC have been reported today, but the exact mechanism is still unclear. Therefore, further research should focus on the pathogenesis and molecular mechanism of MPC.

Keywords: Synchronous triple primary cancers, gastric adenocarcinoma, transverse colon adenocarcinoma

Introduction

Synchronous tumors are second or more tumors occurring simultaneously or within 6 months after the diagnosis of the first tumor. Multiple primary malignant tumors in a single patient are relatively rare. Based on the relevant literature review, the overall occurrence rate of multiple primary malignancies is estimated to be between 0.73 and 11.7% [1]. Although adenocarcinoma is the most common cancer of gastric and colon, but triple primary gastric and colon cancers are extremely rare. In this report, we present our unique case of synchronous triple cancers occurring in the stomach and transverse colon, and discuss the pathogenesis, prognosis and treatment of these concurrent triple cancers.

Case report

A 58-year-old man presented with upper quadrant abdominal pain lasting for 9 months accompanied by nausea and vomiting, it could be alleviated by oral administration of cimetidine, but the patient complained of these recurrent symptoms for the last 4 weeks and said that it could not be alleviated by drugs. He also reported a history of duodenal ulcer and hepatitis B. He did not report any operation history, hypertension, diabetes etc. He also denied any change in appetite or weight. There was no any history of gastrointestinal malignancies in his family. There were no positive findings through physical examination. First, a gastroscopy examination was performed and found there was a 1.0 × 0.8 cm sized ulcer located in the junction of antrum and body (**Figure 1A**). Then, flexible colonoscopy was performed and showed a tumor and multiple polyps of colon (**Figure 1B**). Meanwhile, pathological findings revealed adenocarcinoma in gastric mucosa and high-grade intraepithelial neoplasia in colon. Abdominal contrast-enhanced CT scan revealed there was an ulcerative mass at transverse colon (**Figure 2**). His liver function tests and chemistry panel were within normal limits. However, blood routine examination revealed anemia. Red blood cell count was 4.7/mL (reference range 4.3-5.8/ml), hemoglobin 10.8 g/dl (reference range,

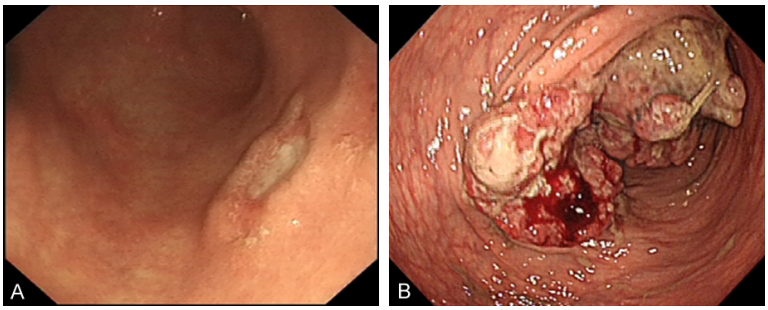

Figure 1. Endoscopic findings. A: Early gastric cancer type IIc lesion at the junction of antrum and body, posterior wall of stomach; B: Ulcerative mass at transverse colon, diagnosed with adenocarcinoma.

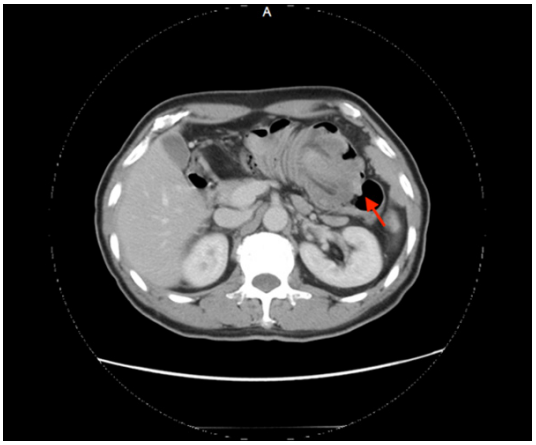

Figure 2. Computed tomography findings. Focal irregular wall thickening at transverse colon with lymphadenopathy, suggesting adenocarcinoma.

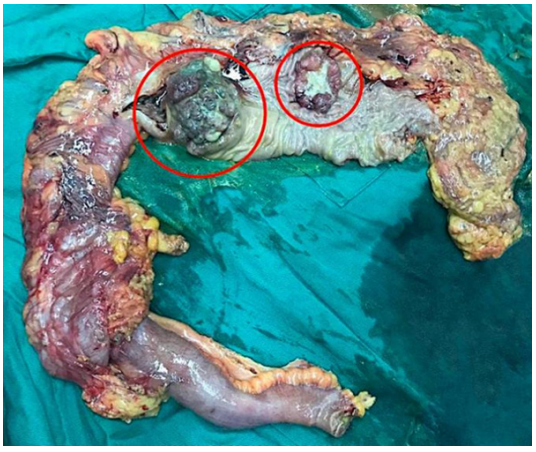

Figure 3. Gross features of the colon cancers. Two protruded type primary cancers, 7.0 × 5.0 cm, 3.0 × 3.0 cm in size respectively, located in the right transverse colon.

13-17.5 g/dl) and hematocrit was 36.2% (reference range 40-50%). Prostate Specific Antigen (PSA) level was 16.3 ng/mL (reference range, 0-4 ng/ml), and carbohydrate antigen 72-4 (CA 72-4) was 19.05 U/mL (reference range, 0-9.0 U/mL). Based on the above examinations, this patient had two synchronous cancers, including gastric cancer and colon cancer. After the discussion of multidisciplinary team (MDT) groups, endoscopic assisted high-frequency electro-excision of multiple colonic polyposis was performed primarily. Then, the patient underwent right hemicolectomy and radical gastrectomy (distal gastrectomy with D2 lymphadenectomy) synchronously. However, during the operation, we found there were actually two masses of transverse colon cancer which were separate from each other, and the operation was very successful. Macroscopic findings from the resected distal stomach indicating IIc type gastric cancer, 1.0 × 0.8 cm in size, in the junction of antrum and body. The specimen gained from the hemicolectomy had two cancers at the right transverse colon, one was 7.0 × 5.0 cm sized, and the other proximal one was 3.0 × 3.0 cm sized, both were protruded type (**Figure 3**). Postoperative pathology confirmed a moderately differentiated gastric adenocarcinoma infiltrating to the submucosa with no metastasis in 19 lymph node (**Figure 4A**). The results of immunohistochemistry: CerbB-2 (1+), Ki-67 (+40%). The TNM classification was defined as $T1_bN0M0$; stage IA. Results from analysis of the transverse colon showed a mucinous adenocarcinoma, with a depth of invasion into the adventitia (**Figure 4B**), and another proximal one was a moderately differentiated adenocarcinoma infiltrating to the adventitia, within no lymph node metastasis (**Figure 4C**). Both of their TNM classification was defined as T3N0M0; stage IIA. The patient was discharged from hospital on postoperative day 26 and received adjuvant chemotherapy for six months according to the regimen, FOLFOX (Oxaliplatin, 5-fluorouracil (5-FU) and leucovorin) for colon cancer.

Discussion

Multiple primary cancers were first reported by Billroth [2] in 1889, but his diagnose criteria was complicated. After that, definition pub-

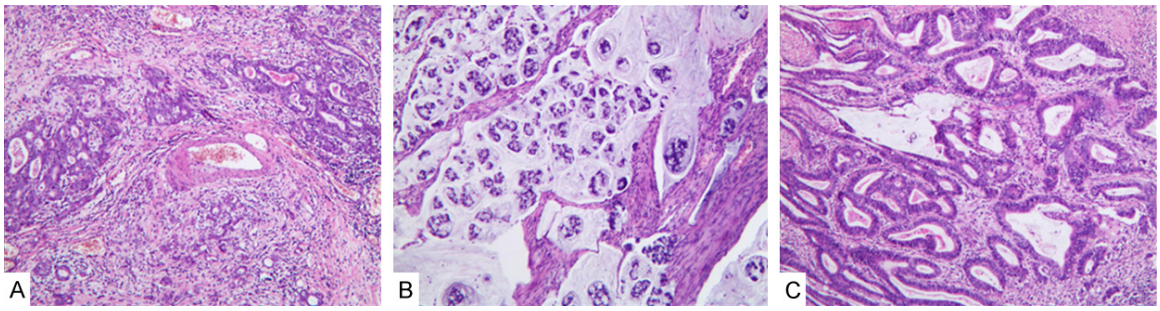

Figure 4. Histopathological findings. A: The resected specimen from the stomach showed a moderately differentiated adenocarcinoma with invasion to submucosa (HE, ×100); B: The resected specimen from the transverse colon showed mucinous adenocarcinoma with invasion to the adventitia (HE, ×100); C: Another resected specimen from transverse colon showed moderately differentiated adenocarcinoma with invasion to the adventitia (HE, ×100).

lished by Warren and Gates in 1932 was widely accepted [3], MPC are defined if the following 3 criteria are satisfied: (1) each tumor must present a definite feature of malignancy, (2) each must be histological distinct, (3) the chance of one being a metastasis of the other must be excluded [4, 5]. Multiple primary cancers may be synchronous or metachronous depending on the interval between their diagnoses, synchronous malignancies are defined as more than two primary cancers occurring simultaneously or 6 months after diagnosis of the first tumor, while metachronous malignancies are subsequent tumors discovered over 6 months after the original cancer [6]. In our case, through three malignances gathered at the gastric and transverse colon, two pathologists carefully checked the slices and found there were precancerous lesions in the junction of cancer and normal tissues, indicating they were primary rather than metastatic tumors. The two colon cancers were derived from independent polyps and there was a normal tissue area of 4 cm between them, excluding the possibility of metastasis and infiltration. Moreover, the malignant features of each tumor were synchronously proven by biopsies. Therefore, this case accords to the criteria.

Nowadays, the morbidity of multiple primary cancers is arising, reports of multiple synchronous primary cancers have increased owing to population aging; improvements in diagnostic techniques [7]; hereditary factors [8]; family history [9]; environmental factors including consumption of tobacco and alcohol [10], and radiation therapy or chemotherapy for primary cancer [11]. In addition to the above factors, microsatellite instability (MSI) is also associated with development of MPC. It was reported that MSI occurred more frequently in cases of MPC than in sporadic cancers [12]. Moreover, Hayashi et al. [8] carried out a study and revealed that 23% of the colorectal cancer patients with accompanying stomach cancer showed MSI while 8% of primary colorectal cancer patients showed MSI. Recently, Cho I et al. showed gastric cancer patients over the age of 60 years or with microsatellite instability-high status were associated with double primary malignancy [13]. Although the study of MPC is more, however, the exact pathogenesis has not been well defined yet.

Recently, lots of studies demonstrated that patients with colorectal cancer (CRC) were likely to develop MPC [14-16]. Also, it was reported that in patients with gastric cancer, the prevalence for associated tumors varies between 2.8% and 6.8% [17, 18]. A research by Kato T et al. demonstrated that among the 1,111 patients with primary CRC, there were 117 patients (10.5%) with MPC, of 18 organs noted to have MPC, malignancies in the stomach were most frequently associated with CRC [19]. Another study by Lee et al. showed that the incidence of synchronous cancer in gastric cancer patients was 3.4%, with the most common synchronous sites being colorectal cancer (37.2%), followed by lung cancer (18.6%), esophageal cancer (16.8%), liver cancer (9.7%), and kidney cancer (4.4%) [20]. To sum up, the malignant tumors accompanying colorectal cancer most frequently were stomach cancer.

MPC are likely to be misdiagnosed, because some malignant tumors have obscure symptoms. In this case, considering that the patient told a long-term diarrhea, we performed a colonoscopy and found the colon tumor. Otherwise, we may have misdiagnosed this case. Therefore,

it is important for us to keep in mind the possibility of multiple primary cancers during the preoperative whole body examination. Currently, as the type of MPC is varies [21]: multiple lesions in the same organ; multiple lesions in different organs; or the combination of the previous two cases, there were no universally accepted standard therapies for MPC. But there were some criteria we may follow. One of the most import factors when deciding the best treatment modality for MPC patients is the stage of each synchronous cancer [22, 23]. The treatment mainly includes curative surgical resection of each cancer, radiotherapy and chemotherapy. And the most common method is surgery associated with adjuvant treatment [24], but in surgically unresectable tumors, the chemotherapy that targets the two tumors and concentrates on the most aggressive seems the most effective treatment [25]. Thus, to improve the long-term prognosis, it is important to perform complete resection for multiple organ tumors. However, this may require multiple operations or large incisional surgery because of the need to approach several organs, which is very invasive for patients. In the current case, after a sufficient pre-operation preparation, we performed an endoscopic assisted high-frequency electro-excision of multiple colonic polyposis. Then, the patient underwent radical gastrectomy (distal gastrectomy with D2 lymphadenectomy) and right hemicolectomy simultaneously as the two malignant colonic lesions were both located in right transverse colon.

The survival rate of the patients with synchronous or metachronous cancer was analyzed by Ikeda et al., they reported that 10-year survival rate was 69.3% in patients without any other primary cancers, 40.1% in synchronous group, and 75.2% in metachronous group [26]. According to the previous research, whenever a synchronous cancer is established, the prognosis is usually determined by the cancer with higher malignant degree [24]. Therefore, in our opinion, to improve the long-term prognosis, it is important to diagnose earlier and choose a correct therapeutic schedule. Nowadays, it was reported that multidisciplinary discussion seems capable of determining optimal uniformity of diagnostic and therapeutic management, and hopefully producing more positive clinical outcomes [27, 28].

In conclusion, doctors should consider the possibility of multiple primary cancers before surgery for gastrointestinal tract malignancies, especially those patients with high risk factors. It is essential to perform full preoperative evaluations including esophagogastroduodenoscopy, colonoscopy, CT scan, PET/CT, and other imaging modalities, if needed. So that the diagnostic rate may be elevated. The stage of each malignancy is the most important factor to determine treatment options for MPC patients. Although many risk factors have been proposed, but the molecular mechanism of MPC is still unclear, more detailed mechanism research needed to be done in the future. Furthermore, prolonged follow-up after surgery should be performed.

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Disclosure of conflict of interest

None.

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