

# Occurrence of metachronous multiple primary cancers occurred in different parts of the stomach with 2 pathologic features

## A case report

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### Abstract

**Rationale:** With the increasing survival rate of gastric cancer, more multiple primary cancers (MPC) have been reported. However, few cases involve metachronous multiple primary cancers which both occurred in the stomach.

**Patient concerns:** An 83-year-old Chinese male had been diagnosed with gastric cardia cancer and underwent proximal gastrectomy. The pathological result was gastric adenocarcinoma. 13 years later the patient's gastroscopy result deteriorated. The biopsy of the antrum revealed dysplasia with doubtful focal cancerization.

**Diagnoses:** Metachronous multiple primary cancers in the stomach.

**Interventions:** Endoscopic submucosal dissection (ESD) was performed. The pathological result showed an intra-mucosal signet-ring carcinoma.

**Outcomes:** After treatment, the patient is alive with good condition until now.

**Lessons:** This is an unusual case of MPC with different pathological features in different parts of the same organ in an interval of more than ten years and undergoing different operations.

**Abbreviations:** CIK = cytokine-induced killer cells, EGC = early gastric cancer, ESD = endoscopic submucosal dissection, GC = gastric cancer, JCGC = Japanese Classification of Gastric Carcinoma, LAK = lymphokine-activated killer cells, MC = metachronous cancers, MGC = metachronous gastric cancer, MPC = multiple primary cancers, SC = synchronous cancers.

**Keywords:** endoscopic submucosal dissection, gastric carcinoma, histological type, lymph node metastasis, metachronous multiple primary cancers

## 1. Introduction

Gastric cancer (GC) is the fourth common cancer in the world and the mortality ranks second.<sup>[1]</sup> The development of diagnostic techniques and the increasing understanding of diseases has improved the detection rate of early gastric cancer (EGC). In addition, due to the application of multimodal treatments, the survival rate of GC has been also improved in recent two decades.<sup>[2]</sup> Therefore, the possibility of GC patients to have

multiple primary cancers (MPC) also improved. The rate of multiple primary GC has been reported to range from 3.4% to 8.2%.<sup>[3–5]</sup> However, the incidence of metachronous gastric cancer (MGC) and the appropriate treatment have not been determined until now, especially if MPC occur in the same organ. In this article, we report a case of early gastric signet-ring cell carcinoma treated by endoscopic submucosal dissection (ESD) after proximal subtotal gastrectomy operation due to gastric adenocarcinoma 13 years ago. This case is an example of the different MPCs in different parts of the same organ after more than 10 years and undergoing different operations.

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Both YS and NZ are cofirst authors.

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## 2. Methods

As this manuscript is a case report, the ethical approval was not necessary.

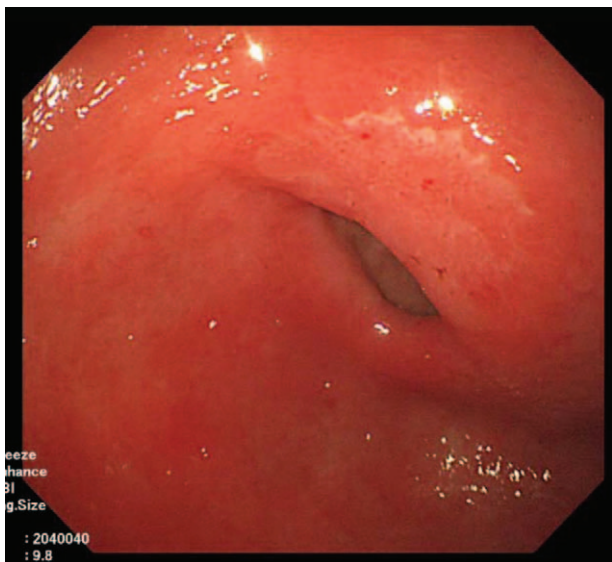
The informed consent was obtained from the patient.

## 3. Case report

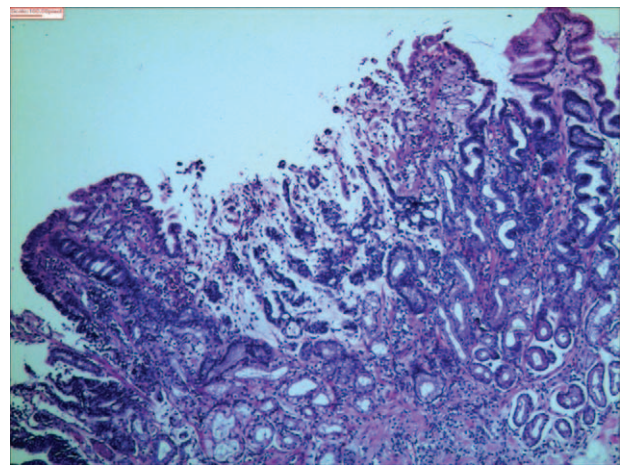
An 83-year-old Chinese male had been diagnosed with gastric cardia cancer in October 2001 and underwent proximal gastrectomy. The tumor was located in the lesser curvature near the cardia with ulcer found and its size was 35 × 40 × 15 mm. The pathological result of the postoperative specimen showed invasion of serosa, but the resection margin and spleen were free of tumor cells. Only the lymph node in lesser curvature was positive, while others were negative. Histological type of the

tumor was gastric adenocarcinoma. Final pathological TNM classification was T3N1M0, and the stage was IIB according to the Japanese Classification of Gastric Carcinoma (JCGC).<sup>[6]</sup> He received adjuvant chemotherapy for 3 times during the following several months. However, chemotherapy was interrupted after these courses due to severe side effects. After discharge, the patient underwent annual or biannual follow-ups with gastro-scope examinations. Meanwhile, he has been receiving cancer biotherapy after operation. During the first 3 years after surgery, the patient received LAK (lymphokine-activated killer cells) therapy ( $5-10 \times 10^9$  cells per course, 4 courses per year). Then, he received CIK (cytokine-induced killer cells) therapy ( $5-10 \times 10^9$  cells per course, 4 courses per year) instead of LAK therapy. During the following years, the gastro-scope results showed no other special performance except the anastomotic erosion and the patient was in a good condition.

However, the patient's gastro-scope result deteriorated subsequently in October 2014. Endoscopy showed a small superficial depressed lesion ( $8 \times 10$  mm) in the antrum of the stomach (Fig. 1). The biopsy revealed dysplasia with doubtful focal cancerization (Fig. 2). In November 2014, he was admitted to our hospital for further treatment. The gastro-scope showed there was a  $20 \times 15$  mm slightly depressed lesion without ulcer and the watershed area was clear with the method of indigo carmine staining (Fig. 3). Then, ESD was performed. The pathological result showed intramucosal signet-ring cell carcinoma (Fig. 4). The carcinoma was visible at the anal margin of the specimen, which was removed by the ESD pathologically and the rest margins were free of carcinoma. Thus, we diagnosed the lesion T1N0M0 and the stage was IA in accordance with JCGC. As intramucosal carcinoma was visible in anal margin, the PET-computed tomography (CT) examination was performed after ESD. It showed that the gastric wall of antrum was slightly thickened and concentration of radionuclide was visible. This prompted that the local metabolism was increased and the suspicious lesions remained. The result did not show concentration of radionuclide in the other organs. According to the result of pathology and PET-CT above, the patient received the second ESD treatment in December 2014. The pathological result of the



**Figure 1.** In October 2014, endoscopy showed a small superficial depressed lesion ( $8 \times 10$  mm) in the antrum of the stomach.



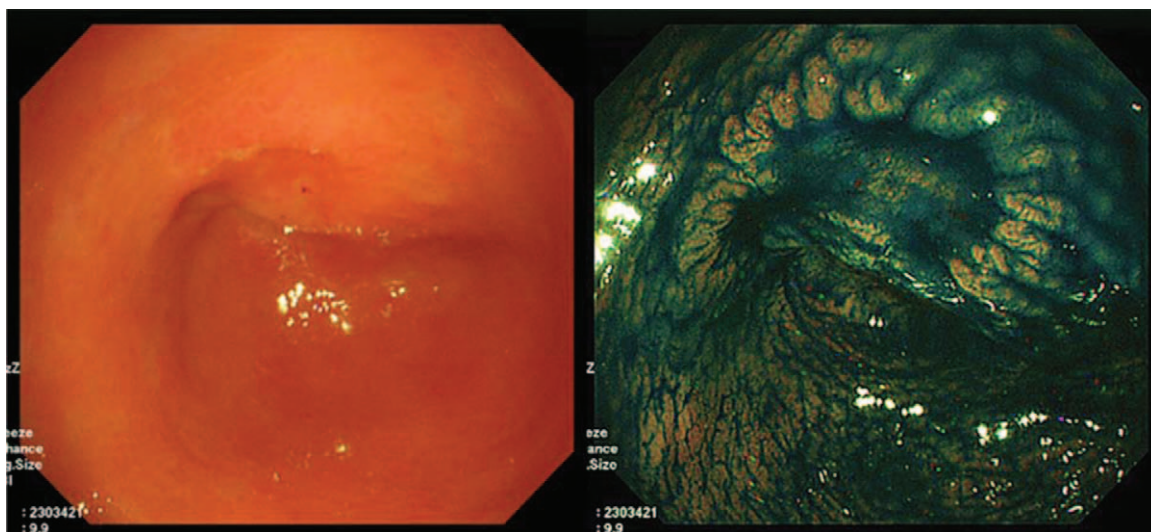
**Figure 2.** In October 2014, the biopsy specimen of antrum revealed poorly differentiated adenocarcinoma. This lesion is only seen in the mucosa.

specimen that was removed by the second ESD showed low grade intraepithelial neoplasia only. After treatment, neither chemotherapy nor cancer biotherapy was given to the patient. He just underwent follow-ups with gastro-scope examinations. He is alive with good condition until now and gastro-scope examinations was normal.

#### 4. Discussion

Since Billroth reported rare cases about MPCs for the first time in 1869,<sup>[7]</sup> people have paid more attention to MPC. Due to the development of medical technology, the detection rate of MPC is significantly increased these years. The criteria for the diagnosis of MPC are not completely unified, but the majority of studies tend to follow the criterion worked out by Warren in 1932. He proposed that each doubtful primary tumor must be clearly evaluated for malignant histologically; must be separated by normal appearing mucosa in the position and own their distinct pathologic features; and we should exclude the possibility that the second neoplasm was a metastasis.<sup>[7]</sup> In addition, according to the diagnostic criteria proposed by Kaspisnow R, synchronous cancers (SCs) are diagnosed within 6 months interval, while metachronous cancers (MCs) are within an interval of more than 6 months. This patient had been diagnosed with gastric cardia adenocarcinoma, and 13 years later, signet-ring cell carcinoma occurred in the antrum. So, we consider that this case is metachronous MPCs in the same organ depending on the above criteria, confirmed by operation and pathology.

At present, many studies have reported MPCs. Yoshino et al<sup>[8]</sup> reported the first study of synchronous and MCs in patients with GC. The incidence of MPC has been reported in a range from 3.4% to 8.2%.<sup>[3-5]</sup> Kim et al<sup>[9]</sup> analyzed 5778 patients with GC. Their study showed the incidence of synchronous double primary cancers and metachronous double primary cancers was 5.0% and 3.7%, respectively.<sup>[9]</sup> However, the reported MPC mostly occurred in different organs and few studies about MPC have investigated in the same organ. The study from Ueno et al<sup>[10]</sup> reported that among 203 (5.4%) MPCs in the stomach, there were 76 (2.0%) patients whose 2 cancers were both in the stomach. MPC mainly occurred in digestive system. Many studies have got similar conclusion that the most common MPC is colorectal cancer, followed by lung cancer and liver cancer.<sup>[4,9,11-13]</sup> The tumors of this case are both located in



**Figure 3.** In November 2014, endoscopy showed a 20 × 15 mm slightly depressed lesion without ulcer. The watershed area was clear with the method of indigo carmine staining.

the stomach where the first one was in cardia and the second was in antrum. This is an unusual case of MPC with different pathological features in different parts of the same organ in an interval of more than 10 years and undergoing different operations.

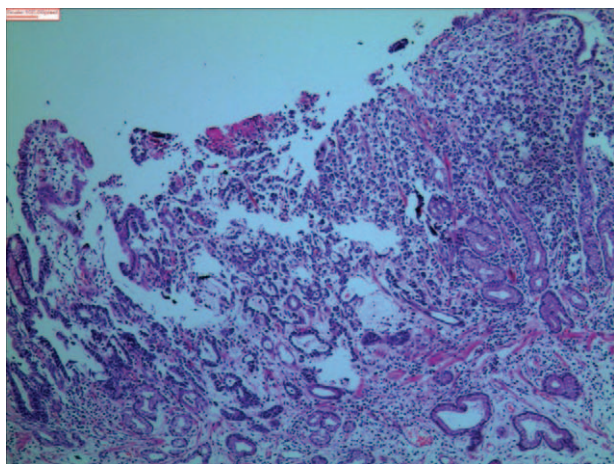
Recently, the incidence rate of MPC is significantly increased. People begin to consider different mechanisms involved in MPC. The studies from Moriwaki and Miyoshi<sup>[14]</sup> and Miyoshi et al<sup>[15]</sup> showed that microsatellite instability (MSI) in multiple primary GCs was significantly higher than single GC. DNA methylation may be one of important causes of carcinogenesis.<sup>[16]</sup> Yamamoto et al<sup>[17]</sup> found loss of protein expression of human mutL homolog 1 (hMLH1) and human mutS homolog 2 (hMSH2) with double primary carcinomas of the stomach and colorectum may play an important role in carcinogenesis. It was also reported that the eradication of *Helicobacter pylori* after endoscopic resection of EGC decreased the incidence of MGC.<sup>[18]</sup> In addition, MPC may

be related with individual susceptibility, smoking, immunodeficiency, heredity, and environmental factors.<sup>[19]</sup>

Diagnosis of MPC in digestive system mainly depends on the clinical manifestations, imaging, endoscope, and pathology. During these years, thanks to the application of endoscopy, the detection rate of GC, especially EGC, is greatly improved. New technologies such as magnifying endoscopy and narrow band imaging (NBI) make it possible to observe the shape and color of the lesion in the stomach more clearly. Meanwhile, endoscopic biopsy can also improve the detection rate. In this case, we found the lesion in the antrum and did biopsy, which showed dysplasia with doubtful focal cancerization pathologically. So, endoscopy could be regarded as one of the basic examinations for diagnosis. In recent years, the PET/CT has become an effective examination to diagnose the malignant tumor. Several studies have showed that the specificity of PET/CT is higher than CT in the detection of lymph node metastases.<sup>[20,21]</sup> The PET/CT of this patient did not show concentration of radionuclide in lymph node and the other organs. Therefore, we consider this case as gastric multiply primary cancers.

There was significant difference in the treatment between MPCs and the recurrence or metastasis of primary cancer. So, it is important how to identify them. The main therapy for MPC in the digestive system is radical operation combined with radiotherapy and/or chemotherapy, which is similar to the single primary cancer. In contrast, the palliative treatment is usually regarded as the first choice for recurrence or metastasis.

In recent years, with the development of endoscopic technology, some of the early primary cancer in upper digestive tract can be resected under endoscope. As ESD displays lower complication rates and shorter hospital stay durations than surgery,<sup>[22,23]</sup> preserves postoperative gastric function, and allows the patient to maintain a better quality of life,<sup>[24]</sup> it is recommended as the standard treatment for some selected cases of EGC. Kasuga et al<sup>[25]</sup> had reported ESD could be a feasible and safe option for synchronous EGC. Isomoto et al<sup>[26]</sup> reported most metachronous lesions were intramucosal tumors without lymphovascular involvement and lymph node metastasis, which indicated the potential of additional ESD rather than gastrecto-



**Figure 4.** In November 2014, the pathological result showed a moderately to poorly differentiated intramucosal carcinoma with multifocal signet ring cell features seen. This lesion is only seen in the mucosa.

my. As a result, in this case when we found the 20 × 15 mm slightly depressed lesion without ulcer in the antrum and the biopsy showed dysplasia with doubtful focal intramucosal cancerization, in consideration of his age, we proposed that ESD could be considered first.

The prognosis of metachronous MPC is also related with the interval time. Tichansky et al<sup>[27]</sup> reported the second cancer was mostly discovered within 1 to 3 years, on average 5 to 7 years. Dinis-Ribeiro et al<sup>[3]</sup> also reported that at least in half of the patients, the median time interval to MC was 3 years (range, 1–22 years). Ren et al<sup>[28]</sup> reported the second cancer usually appeared within 10 years, especially 3 to 5 years. The shorter interval time of metachronous MPC is, the worse the prognosis is. Recurrence or metastasis may also run up to the peak time within 3 years after the treatment for first cancer. So, we should not easily think the second cancer as recurrence or metastasis; as a result, we make the incorrect conclusion leading to delayed treatment. It is necessary to pay close attention to these patients who have the first primary cancer especially in 3 years after the treatment for the first cancer. In this case, the interval time of the metachronous primary cancers was 13 years. Thus, performance of regular follow-up for a longer period of time on patients who have primary GC is still necessary. With the long-term follow-ups, we seasonably found the second primary GC was EGC and performed ESD as soon as possible preventing the early cancer continued to progress. To discover the lesions in early stage contributes to early diagnosis and treatment, which can improve the prognosis. The prognosis of EGC is favorable in general, and a 5-year relative postoperative survival rate of more than 90% has been reported.<sup>[29]</sup> We will go on follow-up his subsequent condition.

In conclusion, from the case and a review of the literature, it appears that people who have 1 malignant tumor might have a higher risk to develop a second one. In GC patients, when endoscope examination is performed, physicians should improve the awareness and vigilance of MPC. In order to avoid missed diagnosis, endoscopic inspection should not be only satisfied with the detection of a cancer center. It is necessary to make efforts to find the suspicious lesions through extensive and careful inspection. When necessary, other examination methods could be used to aid in the diagnosis, such as PET-CT. After gastrectomy or ESD, periodic follow-ups should be carried out to find potential lesions. The distinction between MPC and recurrence/metastasis is difficult and the treatments are different. So, once MPC is diagnosed, we should choose the appropriate treatment in order to avoid condition delayed. In the future, further studies on the pathogenesis and pathology characteristic of MPC in the same organ should be investigated.

## Author contributions

**Data curation:** Yan Song, Ningning Zhao.

**Methodology:** Zhongqing Zheng, Dalu Kong.

**Supervision:** Bangmao Wang.

**Visualization:** Shu Li.

**Writing – original draft:** Yan Song, Ningning Zhao.

**Writing – review & editing:** Kui Jiang.

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