

## Case Report

# Synchronous double primary gastric and endometrial cancer: a case report and literature review

Mingxu Da<sup>1\*</sup>, Lingzhi Peng<sup>2\*</sup>, Yongbin Zhang<sup>1</sup>, Jibin Yao<sup>1</sup>, Yaoxing Duan<sup>1</sup>, Yanghui Wen<sup>2</sup>

<sup>1</sup>Department of Surgical Oncology, Gansu Provincial Hospital, Lanzhou 730000, Peoples Republic of China;

<sup>2</sup>Department of Surgery, Ningxia Medical University, Yinchuan 750000, Peoples Republic of China. \*Equal contributors.

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**Abstract:** Multiple primary malignant neoplasms (MPMN) are two or more malignancies in an individual without any relationship between the tumors. In recent years, increasing number of cases were reported. However, Synchronous double primary gastric and endometrial cancer are relatively rare to be reported. Here we present a rare case of synchronous double cancer involving the stomach and endometrium, which is resected simultaneously and received six times chemo. After reviewing lots of literatures at home and abroad, we discuss the risk factors, the diagnostic criteria, the treatment modalities and the prognosis of these rare MPMN. Although a number of risk factors have been proposed in a mass of literatures, but the mechanism of MPMN is still unclear. We didn't discover a detailed explanation for the mechanism of MPMN from our patient. Therefore, further research should focus on the etiology and mechanism of MPMN.

**Keywords:** Synchronous, multiple primary malignant neoplasms (MPMN), gastric cancer, endometrial cancer

## Introduction

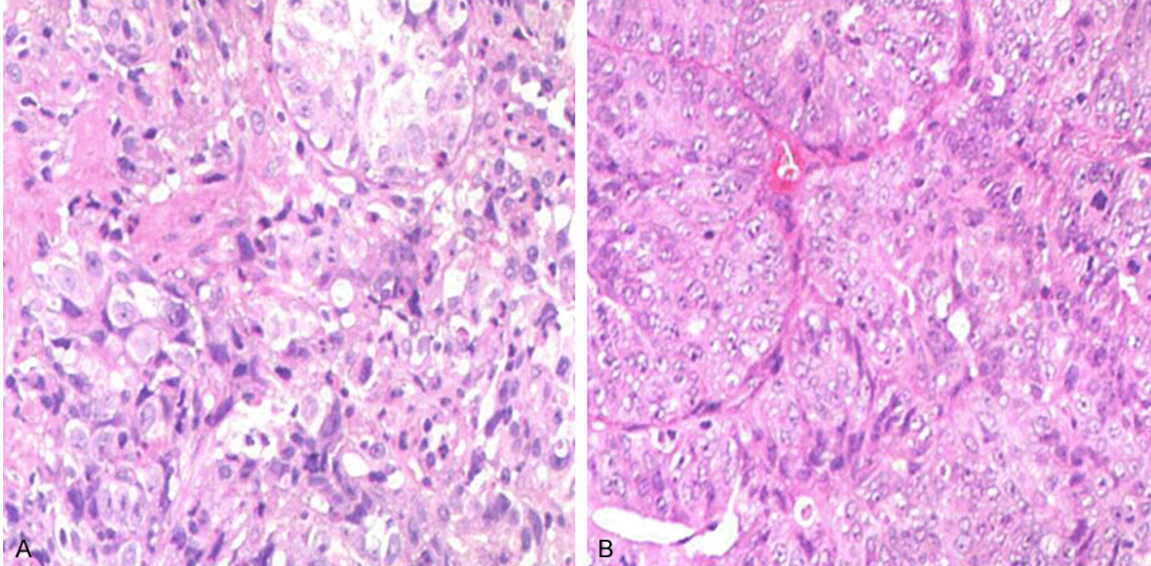
Multiple primary malignant neoplasms (MPMN) are two or more malignancies in an individual without any relationship between the tumors. Increased survival of cancer patients, the growing life expectancy and the development of improved diagnostic techniques, have all contributed to the increased frequency of MPMN [1]. The incidence of MPMN has been concluded by a literature review on 1,104 269 cancer patients, and ranged from 0.73% to 11.7% [2], double primary gastric and endometrial cancer is extremely rare. Furthermore, the cases of synchronous double gastric and endometrial cancer have not yet been reported. Here, we report a case of synchronous double cancer involving the stomach and endometrium, which was successfully resected simultaneously.

## Case report

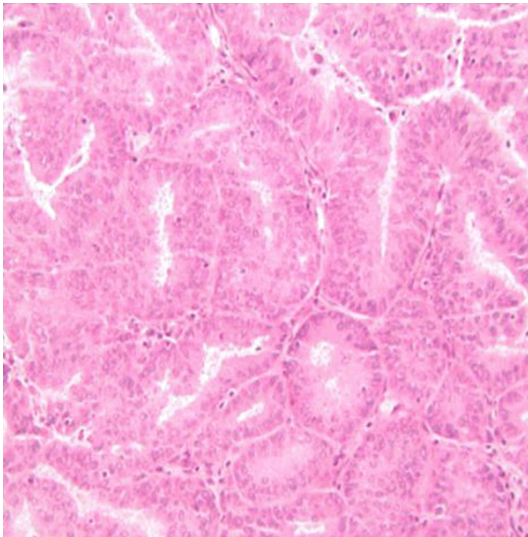
A 49-year-old woman visited a local hospital due to five-year history of repeated malaise of pain attack in the epigastrium and one-year history of the above symptom aggravating

associated with loss of weight (about 5 kg). As a gastroscopy and biopsy demonstrated gastric cancer, the patient was referred to our hospital (Gansu province people hospital, China), for further examination and treatment. His past surgical history consisted of only a stripping of the great saphenous vein for varicose veins in the great saphenous vein. Gastroscopy in follow up after admission showed that there was an enormous ulcer in posterior wall of gastric body, gastric body mucosa is rigid and its surface covered with yellow-white moss, and local eminence of gastric mucosa. Endoscopic biopsy from the stomach revealed adenocarcinoma (**Figure 1A**). Gynecological ultrasound examination showed endometrial thickening with echo owe evenly, and found a Naboth cyst and a small amount of fluid accumulation in the cavum Douglasi. Vaginal ultrasonography revealed endometrial thickening measuring 21 mm, multiple Naboth cyst, and an ovary cyst measuring 27×18 mm at left side in pelvis cavity. Spiral CT epigastric enhancement scanning revealed wall thickening of gastric body with moderate, homogeneous enhancement. Spiral

## Synchronous double cancer in an individual



**Figure 1.** The biopsy results from preoperative specimens. A: Endoscopic biopsy from the stomach revealed adenocarcinoma; B: The biopsy from the endometrium endometrial adenocarcinoma.



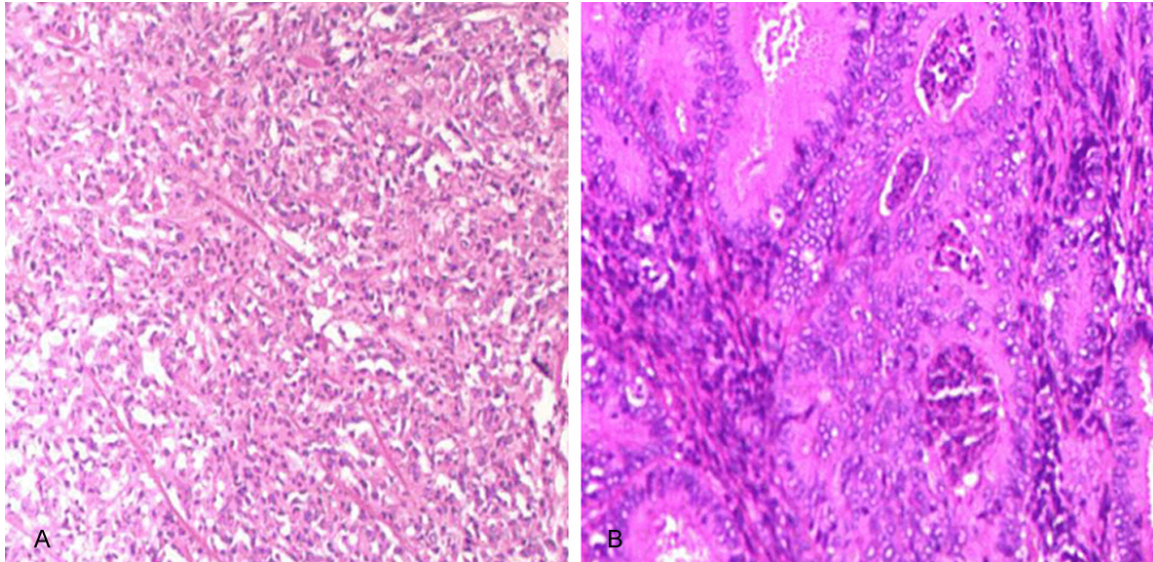
**Figure 2.** Intraoperative frozen section examinations from the endometrium showed endometrial severe atypical hyperplasia with cancerous.

CT pelvic enhancement scanning enlarged uterine size, myometrium thickening. The diagnostic uterine curettage were performed, the pathologic result revealed endometrial adenocarcinoma (**Figure 1B**). Carcinoembryonic antigen (CEA) was 1.60 ng/ml. carbohydrate antigen 125 (CA 125) was 12.17 U/ml and carbohydrate antigen 72-4 (CA 72-4) was 1.60 ng/ml. According to the above test result, the patient was diagnosed with synchronous double pri-

mary gastric and endometrial cancer. Laparoscope-assisted radical gastrectomy for gastric cancer (laparoscopic distal gastrectomy with D2 lymphadenectomy) and laparoscopic assisted vaginal hysterectomy with bilateral adnexectomy were simultaneously carried out for the patient; the operation was very successful. Intraoperative frozen section examinations showed endometrial severe atypical hyperplasia with cancerous (**Figure 2**).

The resected specimens from the stomach showed a poorly differentiated adenocarcinoma with deep myoinvasion (**Figure 3A**); the results of immunohistochemistry: CKP (+), EMA (++), ki-67 (>75%), HER2/neu(-). The TNM classification was defined as T2N0M0; stage IB. The resected specimens from the uterus appendages showed: (1). highly to moderately differentiated adenocarcinoma with invasion to 1/6 whole layer of uterus (**Figure 3B**); Cancer cells were also found in the left uterine horn. (2). chronic cervicitis with squamous epithelium and cervical intraepithelial neoplasm (CIN1). (3). Ovary and fallopian were not found no obvious abnormal. The results of immunohistochemistry: ER (+), PR (+), ki-67 (50-75%). Multidisciplinary staff decided a systemic chemotherapy with tegafur, docetaxel and Oxaliplatin, and the patient received six times chemo successfully. Carcinoembryonic antigen (CEA) level, carbohydrate antigen 125 (CA 125),





**Figure 3.** The pathologic result from the resected specimens. A: The resected specimens from the stomach showed a poorly differentiated adenocarcinoma with deep myoinvasion; B: The resected specimens from the uterus appendages showed highly to moderately differentiated adenocarcinoma with invasion to 1/6 whole layer of uterus.

and liver function are normal in the follow-up after one year.

## Discussion

Since the phenomenon of MPMN in a single patient first described by Warren and Gates in 1932 [3], numerous cases have been reported by several authors. In patients with gastric cancer, the prevalence for associated tumors varies between 2.8% and 6.8% [4]. In all gastric cancer patients, the frequency of synchronous malignant tumors has been reported to be 3.4% in 3291 cases by Lee JH et al. [5]. The most common another primary cancer is colorectal cancer, followed by lung and liver cancer [5]. Double malignancies of stomach and gynecologic are relatively rare to be reported. Especially, synchronous gastric and endometrial cancer was hardly reported in the literature.

The majority of scholars comply with Warren and Gates criteria to diagnose MPMN, included the following: (1) each tumor must present a definite picture malignancy; (2) each tumor must be histologically distinct; (3) the possibility that one is a metastasis of another must be excluded. If the time interval between the secondary cancer and primary cancer diagnoses was less than 6 months, the patients were considered to have synchronous tumor (s); if the

time interval was more than 6 months, the tumor (s) were considered to be metachronous [3]. In our patient, the malignant features of each tumor were synchronously proven by biopsies and postoperative pathological diagnosis. And the possibility that one is a metastasis of another have was excluded. Therefore, the case accords with Warren and Gates criteria.

Although the study of MPMN is more, but its pathogenesis is still unclear. The most frequent factors involved are intense exposure to carcinogens, genetic susceptibility, immune system of patients, and carcinogenic effects of radio/chemotherapy used in the treatment of tumors [6, 7]. Carcinogenic effects, such as tobacco and alcohol, may increase the likelihood of multiple independent malignant foci developing in the mucosa epithelium [7]. This phenomenon can be explained by “field cancerization”. In 1953, Slaghter et al. proposed field cancerization, a process whereby the epithelial lining has been continuously exposed to tobacco and/or alcohol, leading to extensive premalignant and malignant cytologic changes and an increased risk for multiple independent tumor development [8]. Furthermore, Braakhuis B and Tabor M, et al concluded by a literature review, organs in which the phenomenon of field cancerization are: squamous cell cancer of the oral cavity, oropharynx and larynx, lung,

esophagus, vulva, cervix, colon, breast, bladder and skin [9]. Many authors believed the phenomenon will occur during aero-digestive tract when mucosa at this level is exposed to the same types of carcinogens, if they act consistently and for a long time [10-12].

Genetic susceptibility have been largely proposed for the development of secondary malignancies in many literatures. There are approximately 100 genes which when mutated are known to predispose to one or more forms of cancer [13]. Mutations in the genes are involved in some genetic syndrome. For example, Lynch syndrome is caused by inherited mutations in at least five different mismatch repair (MMR) genes including MLH1, MSH2, MSH6 and PMS2 [13]. The types of cancer most often associated with this syndrome are colorectal cancers, endometrium, ovary, small bowel, pancreas, biliary and urinary tract [13, 14]. P53 mutations cause Li-Fraumeni Syndrome; an autosomal dominant disorder associated with a high risk of breast cancer, osteosarcoma and soft tissue sarcomas, as well as brain tumors, leukemias and adrenocortical carcinoma in children and young adults [15, 16]. In addition, Clinicians should consider the possibility of other hereditary cancer syndromes (Cowden syndrome, Hereditary breast ovarian cancer syndrome, PTEN hamartoma tumor syndromes, Peutz-Jeghers syndrome, and so on) in patients who have multiple primary cancers [13, 17-19]. Some literatures point out that these syndrome are also associated with MPMN. In addition to the genetic syndromes, microsatellite instability (MSI) is also associated with development of MPMN. MSI has been noticed that occur more frequently in cases of MPMN than in sporadic cancers [20]. Therefore, an individual who is diagnosed with two or more of the characteristic cancers (synchronous or asynchronous) should receive genetic testing. Currently, the new technologies available could analyze various genetic changes. However, these technologies are expensive and are rationed accordingly. Our patient didn't receive genetic testing because of the family history is negative and family economic condition is lower.

Beyond the factors above, the treatment of tumors (radio/chemotherapy) is also associated with MPMN. Travis et al. [21] discovered that radiotherapy alone, chemotherapy alone, and

both, following the treatment of a primary cancer increase risks of second primary cancers. Among testicular cancer patients given radiotherapy alone, risks were significantly elevated for cancers of the stomach, colon, rectum, pancreas, lung, pleura, prostate, kidney, bladder, malignant melanoma, connective tissue and thyroid [21]. The use of tamoxifen in breast cancer patients has been associated with a significantly increased risk of endometrial cancer [22, 23].

Currently, there was no an universally accepted standard treatment for MPMN. The treatment of choice, depending on the tumor location, involved curative surgical resection of each cancer, radiotherapy and chemotherapy [6]. The most common treatment is surgery associated with adjuvant treatment [6]. The treatment for synchronous double cancers was generally based on surgery or chemotherapy, but in surgically non resectable tumors, the chemotherapy that targets the two tumors and concentrates on the most aggressive seems the most reasonable treatment [24]. In our case, laparoscope-assisted radical gastrectomy for gastric cancer and laparoscopic assisted vaginal hysterectomy with bilateral adnexectomy were simultaneously carried out for the patient, and the patient received six times chemo successfully.

The survival rate of the patients with a synchronous or metachronous cancer was analyzed by Ikeda et al., they argued that 10-year survival rate was 69.3% in patients without another primary cancer, 40.1% in the synchronous groups, and 75.2% in the metachronous group [25]. According to the literature, the prognosis of patients with MPMs could be determined independently in function of the stage of each cancer [6]. Early diagnosis and treatment may be the key risk factors affecting prognosis.

In conclusion, although a number of risk factors have been proposed in a mass of literatures, but the mechanism of MPMN is still unclear. We didn't discover a detailed explanation for the mechanism of MPMN from our patient. We need further basic research for the detailed mechanism. Simultaneous multiple primary cancers should try to be removed simultaneously. And adjuvant treatment (radio/chemotherapy) should also be considered. Healthcare workers should consider that the appear-

ance of an additional tumor in a cancer patient may be either a metastatic or novel lesion, and the possibility of a metachronous or a synchronous malignancy should be investigated. Furthermore, prolonged follow-up after surgery should be performed.

## Disclosure of conflict of interest

None.

**Address correspondence to:** Dr. Mingxu Da, Department of Surgical Oncology, Gansu Provincial Hospital, 204 Donggang West Road, Lanzhou 730000, P. R. China. Tel: +86-15095321201; E-mail: hxdamingxu@hotmail.com

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