Multiple synchronous primary malignant neoplasms: A case report and literature review

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Abstract. Multiple primary malignant neoplasms (MPMN) are defined as two or more primary malignancies diagnosed in an individual. There is no association between these cancers, which can be classified into synchronous and heterochronous cancers depending on the time of diagnosis. The present study presented a rare case of bilateral breast, endometrial, cervical and ovarian cancers. Through thorough physical examination, pathology and immunohistochemistry, it could be determined that bilateral breast, endometrial and cervical cancers were primary malignant tumors and that ovarian cancer cannot be excluded as a result of metastasis. The present study also summarized the definitions, risk factors, prevalence characteristics, diagnostic ideas and treatment options for MPMN by reviewing the literature.

Introduction

Multiple primary malignant neoplasms (MPMN) are defined as two or more primary malignancies occurring in the same person, rather than metastasis. So far, numerous (1-6) of MPMN have been reported, with a relatively large number of diachronic MPMN and a smaller proportion of simultaneous MPMN. It is rare to find three or more cases of simultaneous multiple malignancies. Owing to continuous innovations in the treatment of malignant tumors, the survival of some patients with cancer has been prolonged. In addition, because of an increase in human longevity and improvements in diagnostic technology, the incidence of a number of types of malignant tumors is on the rise. The present study reported the case of a 51-year-old woman with right-sided invasive breast cancer, left-sided ductal carcinoma *in situ*, endometrioid adenocarcinoma, cervical cancer and ovarian cancer. Such cases of multiple concurrent primary tumors are rare.

Case report

A 51-year-old woman with a history of mammary gland involvement and no history of cancer or other diseases was admitted to The Second Hospital of Jilin University (Jilin, China) for vaginal bleeding. The approval number of this case are 2023138. Six months before hospitalization, she had experienced vaginal bleeding but did not pay attention to it. Gynecological examination revealed a vaginal tumor 5-6 cm in diameter that appeared in the cervix and accumulated in the lower third of the vagina. Biopsy of the cervical tumor showed a hypodifferentiated neuroendocrine carcinoma with invasive squamous cell carcinoma nests in the local cells (Fig. 1). To clarify the stage and further improve the examination, the brain was scanned using functional magnetic resonance imaging (MRI). Chest, abdomen and pelvis computed tomography (CT) with contrast were subsequently performed, which revealed a cervical lump (Fig. 2A and B), right abdominal lump (Fig. 2C and D), left breast lump (Fig. 2E and F) and right breast lump (Fig. 2G and H). Based on the imaging findings, it was suspected that the lumps were malignant. Therefore, a biopsy of the breast and ovarian masses was performed to obtain pathological tissue. Low-grade ductal carcinoma *in situ* was observed in the pathological tissue of the left breast (Fig. 3A), invasive breast cancer was observed in the pathological tissue of the right breast (Fig. 3B) and invasive carcinoma was observed in the pathological tissue of the right ovary with localized areas of neuroendocrine differentiation (Fig. 3C). For H&E staining, the tumor tissue sections were dewaxed and hydrated. The sections were stained with hematoxylin and eosin staining, respectively. Dehydrate with low to high levels of alcohol. Slices were penetrated with xylene and covered with resin. HE-stained sections were imaged using Leica DM4000B fluorescence microscope (magnification: x100).

Immunohistochemistry was performed on the cervical, bilateral breast and right ovarian pathological biopsy tissues. For immunohistochemical staining, tumor tissue was embedded in paraffin wax and a section of 4-μm thickness was cut using a microtome (HM355s, Thermo Scientific). The slices are dewaxed and hydrated. Heat-induced antigen repair

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was performed with 10 mM sodium citrate buffer (PH 6.0). The activity of endogenous peroxidase was blocked by incubation with 3% H2O2 for 10 min. Penetration was performed in 0.1% Triton X-100. The tissue sections were incubating by PBS-T (QuickBlock™ Blocking Buffer, Beyotime, Shanghai, China) containing 10% goat serum (Beyotime, Shanghai, China) at room temperature for 25 min to block non-specific binding. Primary antibody (Catalogue number, supplier are listed in Table I) is incubated overnight at 4˚C. Add horseradish peroxidase (HRP) labeled goat anti mouse/rabbit IgG, 1:50, (Beyotime, A0216, A0208, Shanghai, China) to slices, and incubation for 30 min at room temperature. Add Diaminobenzidine (DAB) (DAB Horseradish Peroxidase Color Development Kit, Beyotime, P0203, Shanghai, China) to each section and the color was developed 30 sec to 5 min away from light. The staining effect was observed under a microscope, and the staining was terminated with distilled water. Double dye with hematoxylin for 30 sec at room temperature. Photographs are taken under an optical microscope. Immunostained sections were imaged using Leica DM4000B fluorescence microscope (magnification: x100). Immunohistochemistry of cervical tissue was as follows (Fig. S1): CK(AE1/AE3) (+), CK5/6 (partial +), p63 (partial +), P40 (partial +), Pl6 (+), Ki67 (90%+), CgA (-), Syn (weak +), CD56 (partial +). Immunohistochemistry of the left breast tissues was as follows (Fig. S2): ER (+), PR (partial +), CK5/6 (-), HER 2 (2+), Ki67 (10%+), P16 (+), P40 (-), Syn (-), CK (AEl/AE3) (+). Immunohistochemistry of the right breast tissue was as follows (Fig. S3): INSMl (partial +), CgA (-), Nkx2. 2 (-), CK7 (-), CK8/18 (+), nut (-), BRG 1 (+), ER (partial +), PR (-), GATA3 (little +), INI-1 (+). Immunohistochemistry of the right ovarian tissue was as follows (Fig. S4): TTF I 1 (+), Ki67 (95% positive), P53 (-).

Due to the large cervical lump and persistent vaginal bleeding, our treatment team decided to perform external beam radiation therapy (EBRT) to shrink the tumor for surgery. EBRT was started on February 18, 2022 and finished on March 21, 2022. The whole uterus, adnexa and lymphatic drainage area were treated with 50 Gy in 25 fractions, 1.8 Gy per day, 5 days per week, to the planning target volume. Positive pelvic lymph nodes were treated with 60 Gy in 25 fractions, 2.4 Gy per day, 5 days per week, delivered to the planning target volume. In addition, combined chemotherapy, including albumin, paclitaxel, carboplatin and bevacizumab, was administered for three cycles during and after radiotherapy. Gynecological surgery was performed on June 12, 2022, during which the entire uterus and bilateral adnexa were removed. The postoperative pathological findings were as follows: Cervical tissue infiltrated by multiple foam cells, consistent with manifestation after neoadjuvant therapy and, surprisingly, localized cancerous tissue was observed in the endometrium, a highly differentiated endometrioid carcinoma with a maximum diameter of ~5 mm (Fig. 3D). A small number of heterotypic cell nests were observed in the right ovary, consistent with poorly differentiated carcinomas. The patient then underwent three cycles of chemotherapy and radical breast cancer surgery according to the original protocol. She is currently in a good general condition and intends to continue adjuvant treatment for breast cancer.

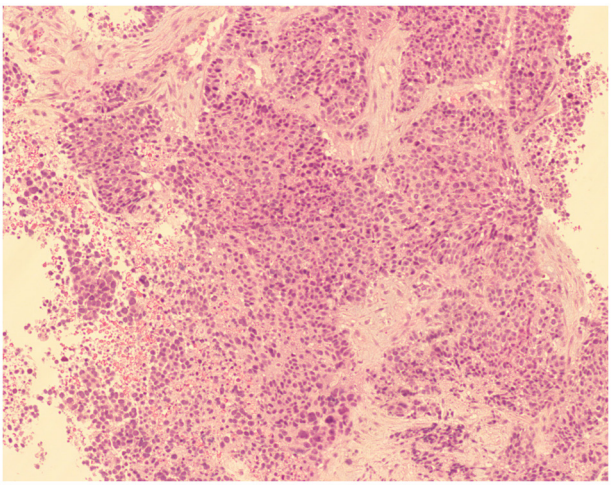

Figure 1. Hematoxylin and eosin staining of cervical site pathological tissue: Poorly differentiated neuroendocrine carcinoma of the cervix with an invasive squamous cell carcinoma nest in a local area. Magnification, x100.

Literature review. MPMN refers to the occurrence of two or more primary malignant tumors in a single patient. It occurs around the age of 50 years, which is similar to the age at which the incidence of malignant tumors is high. It is widely considered that the reasons for the increasing incidence of multiple cancers are multifaceted, such as the increased health awareness of individuals, improved clinical treatment techniques, genetic defects, environmental problems, adverse effects of treatment for the first primary cancer, decreased immune levels due to tumors or treatments and increased life expectancy. With the improvement of the Chinese economy, the realization of early tumor diagnosis and the rapid development of tumor treatment technology, an increasing number of patients with tumors have significantly longer survival times than previously and the incidence of multiple cancers has increased.

The more accepted diagnostic criteria for multiple cancers are those proposed by Warren and Gates (7): i) Each tumor should be histologically malignant; ii) each tumor has unique pathological features; iii) tumors occur at different sites/organs or in different locations in the same organ and iv) patients with mutual metastases or recurrence are excluded. Multiple carcinomas are classified as concurrent or heterochronic multiple carcinomas according to the time of occurrence. Concurrent multiple carcinomas are those that occur within 6 months and multiple heterochronic carcinomas are those that occur for more than 6 months. Metastases can occur within the same organ or between different organs and multiple cancers exhibit this feature. Therefore, in the process of tumor diagnosis and treatment, metastases and multiple cancers should be identified based on a combination of various tumor characteristics, imaging and pathologies to reduce missed diagnoses of multiple cancers.

Coyte *et al* (8) found that the prevalence of multiple cancers is associated with the epidemiological characteristics of the tumor in a country or region. For example, in Japan the most common type of primary MPMN is gastrointestinal malignancy, followed by breast cancer (9). It is reported that the incidence of multiple cancers in patients with primary

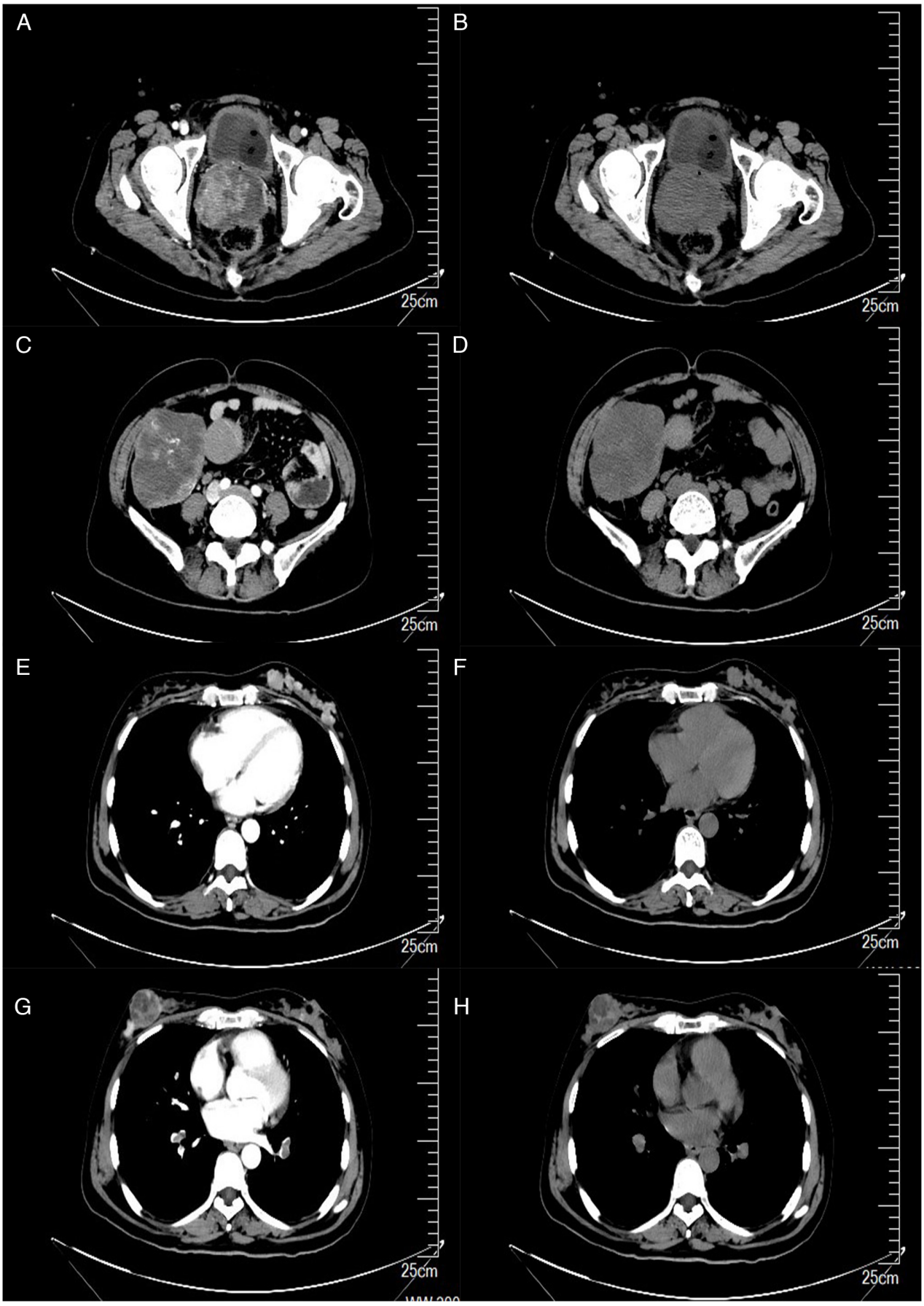

Figure 2. CT images of tumors at four sites. (A) Images of cervical lump on enhanced CT scan. (B) Images of cervical lump on routine CT scan. (C) Images of right abdominal lump on enhanced CT scan. (D) Images of right abdominal lump on routine CT scan. (E) Images of left breast lump on enhanced CT scan. (F) Images of left breast lump on routine CT scan. (G) The images of right breast lump on enhanced CT scan. (H) The images of right breast lump on routine CT scan. CT, computerized tomography.

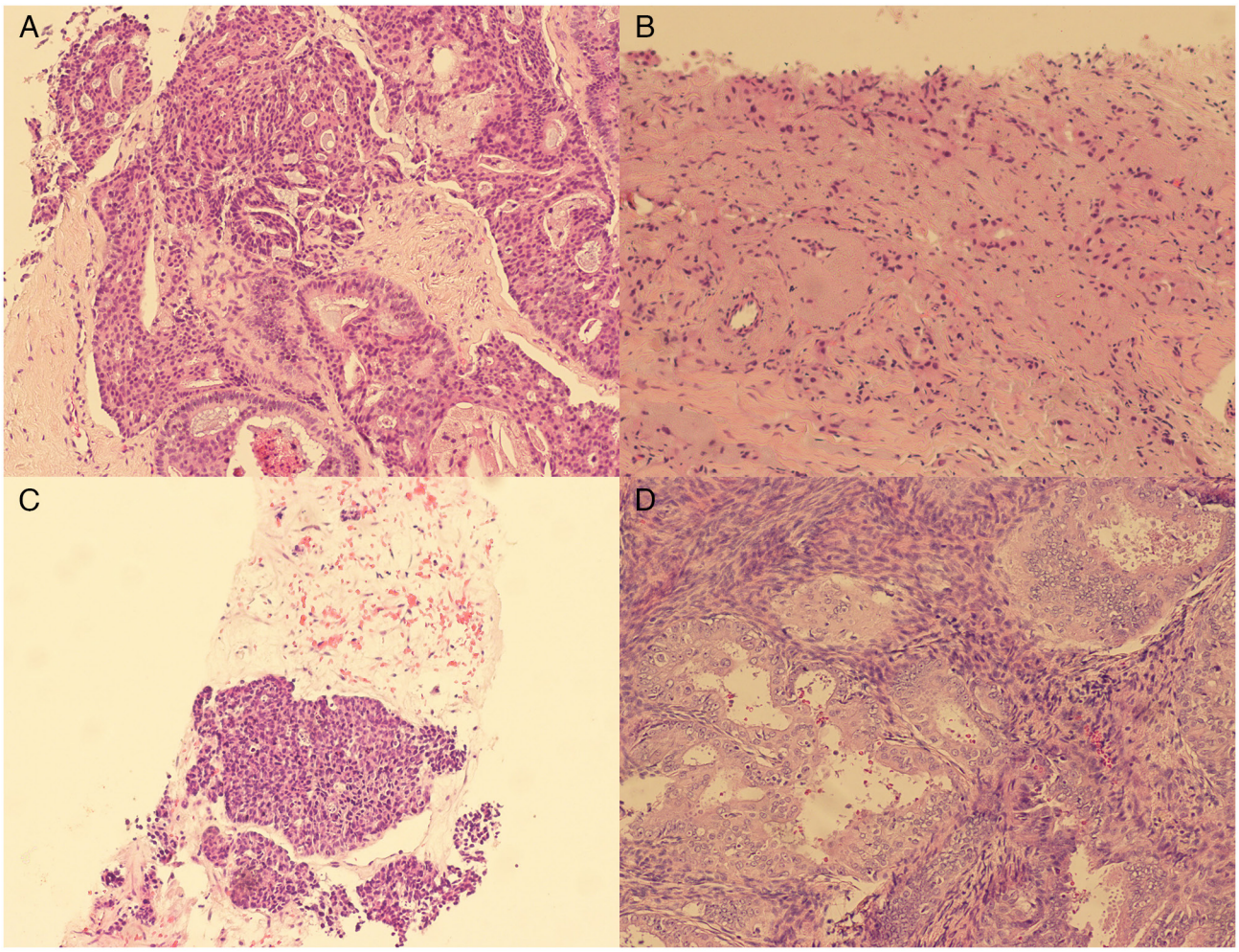

Figure 3. Hematoxylin and eosin staining of other sites of pathological tissue. (A) Ductal carcinoma *in situ* of the left breast. (B) Invasive carcinoma of the right breast. (C) Invasive carcinoma of the right ovary with localized areas of neuroendocrine differentiation. (D) Highly differentiated endometrioid carcinoma with a maximum diameter of ~5 mm. Magnification: x100.

head and neck squamous cell carcinoma can account for 10-40% (10). Adjei Boakye *et al* (11) reported that the incidence of secondary primary carcinoma after treatment for squamous carcinoma of the head and neck ranged from 5-36%. Song *et al* (12) found that the incidence of second primary carcinoma of the oral cavity associated with radiotherapy for nasopharyngeal carcinoma was 0.3-11% and that the tissue type was mostly squamous cell carcinoma. When the first cancer is breast cancer, there are more reports of a second primary cancer occurring in the thyroid (13). A study conducted at the Cancer Hospital of the Chinese Academy of Medical Sciences showed that the most frequent cancers with cervical cancer as the primary cancer were esophageal cancer, followed by bronchial lung cancer, stomach cancer, uterine body malignancy, rectal cancer and breast cancer. In addition, the wide application of radiotherapy for cervical cancer and its treatment effects have been improving and an increasing number of patients are surviving for a long time. Therefore, radiation cancer, a serious long-term complication of radiation therapy, has been identified. Radiation carcinomas account for 23% of repeat carcinomas and 82.2% of repeat carcinomas within the radiated area of cervical cancer (14).

Several factors contribute to the development of multiple cancer types. Therefore, primary prevention of diseases, such as smoking cessation, exercise and good sleep, should be performed. Attention should be paid to secondary prevention strategies including early detection, diagnosis and treatment. In addition, cancer patients have a higher tendency to develop multiple types of cancer. According to statistics, it is estimated that 5-15% of patients develop secondary primary cancer. Therefore, attention should be paid not only to the diagnosis of multiple cancers before the treatment of malignant tumors, but also to regular and comprehensive reviews after treatment. If this can be done, we can avoid missed and mis-diagnoses, which can delay treatment. Clinicians should consider the most common organs involved in multiple cancers. Follow-up reviews of patients with breast cancer should focus on the thyroid and ovaries; patients with nasopharyngeal cancer should pay attention to tongue changes. Patients with cervical cancer can undergo regular esophagoscopy during the review. In all patients with cancer, the possibility that the lung lesion may be a secondary primary cancer should be considered.

Among the theories on multiple cancer risk factors, one is the 'regional carcinogenesis theory', in which researchers consider that the esophagus and gastrointestinal tract are the channels for

Table I. Primary antibodies.

Antibody	Company	Cat. no.	Dilution
Anti-Cytokeratin AE1/AE3	Sigma-Aldrich; Merck KGaA	MAB3412	1:500
Anti-CK5/6	Uni-science	PA6040	1:100
Anti-p63 Rabbit Monoclonal	Sigma-Aldrich; Merck KGaA	SAB56000289	1:50
NCF4/p40-phox Rabbit mAb	ABclonal	A0935	1:200
Anti-ARPC5/p16 ARC	Abcam	ab51243	1:50
Anti-CGA	Sigma-Aldrich; Merck KGaA	HPA029698	1:250
Anti-NCAM1 antibody	Abcam	ab133345	1:500
Anti-Desmuslin/SYN antibody	Abcam	ab204369	1:1000
Ki67 Rabbit mAb	ABclonal	A20018	1:250
ERp44 (D17A6) XP® Rabbit mAb	Cell Signaling	3798	1:500
ERp44 (D17A6) XP® Rabbit mAb	Cell Signaling	8757	1:500
Anti-INSM1	Abcam	ab305104	1:100
NKX2-1 Rabbit mAb	ABclonal	A22247	1:1000
Anti-Cytokeratin 7 antibody	Abcam	ab181598	1:5000
Aiti-CK8/18 antibody	Uni-science	PA7148	1:1000
NUT (C52B1) Rabbit mAb	Cell Signaling	3625	1:3000
Anti-BRG1	Abcam	ab110641	1:100
Anti-GATA3	Abcam	ab199428	1:500
INI-1 (MRQ-27) Mouse monoclonal	Sigma-Aldrich; Merck KGaA	272M-1	1:200
Anti-TTF1	Abcam	ab76013	1:250
p53 Rabbit pAb	ABclonal	A0263	1:50

food, the lungs are the channels for breathing and the urinary system is the channel for waste excretion. After tumor treatment, they continue to receive stimulation from carcinogens, leading to the development of multiple carcinogens (15). Considering that regional carcinogenesis is a continuous and progressive process, it is important to follow patients with relevant tumors for life. In addition, in the clinical treatment process, combined immunotherapy can be considered to reduce toxicity, increase effectiveness, avoid the harm caused by traditional treatments, such as radiotherapy and chemotherapy, and can also enhance the immune ability of patients, control disease development, improve clinical efficacy and prolong and improve the quality of life and survival of patients.

Multiple cancers not only aggravate the condition of cancer patients but also make treatment difficult. Prognosis also differs depending on the location of multiple cancers and treatment methods. Although multiple cancers are difficult to treat, early detection, diagnosis and selection of appropriate treatment methods can still enable long-term survival in some patients. Therefore, once multiple cancers are considered, multidisciplinary consultations should be actively conducted to consider the specific conditions of each patient and to formulate individualized treatment plans to obtain the best treatment and prognosis.

Discussion

The occurrence and reporting of multiple cancers associated with breast cancer is common. Previous case reports (16-21) have identified a number of types of multiple cancers associated with breast cancer, including skin cancer, gastrointestinal cancer, colon cancer, hematologic tumors, sarcomas, lung cancer, gynecologic tumors, thyroid cancer and urinary malignancies (16). There is a close association between breast cancer and gynecological tumors, especially ovarian cancer, because they share similar risk factors such as early menarche, advanced age without childbearing, obesity and high-fat diet (22,23). In addition, some genetic syndromes, such as Lynch syndrome, Cowden syndrome and mutations in the BRCA1 and BRCA2 genes, increase the risk of developing breast, ovarian and endometrial cancers (21,24). Therefore, gynecological examinations should be considered when patients are diagnosed with breast cancer. During follow-up after treatment, attention should be paid to the examination of the ovary and uterus to exclude lesions.

In the present case, pathological tissues were obtained from patients with cervical cancer, bilateral breast cancer, ovarian cancer and endometrial cancer and hematoxylin and eosin staining performed (H&E staining). Cervical malignancies, bilateral breast malignancies and endometrial malignancies are significantly different histologically, which meet the inclusion criteria of Warren and Gates and can be defined as MPMN. To further confirm the origin of these cancerous tissues, immunohistochemical testing was performed on these tissues. P16, CK (AE1/AE3), CD56 were positive, confirming that cervical cancer was primary. Bilateral breast cancer histological morphology is different; estrogen (ER) and progesterone receptors are positive in left breast cancer; ER and insulinoma-associated-1 receptors are positive in right breast cancer. These features confirm

that bilateral breast cancers are primary and that bilateral breast cancers do not metastasize to each other. Endometrial cancer is found after surgery and its histological morphology shows that it is endometrioid carcinoma. Although there is no immunohistochemical support, the diagnosis was confirmed as primary endometrial cancer by three experienced pathologists. Here, cancerous tissue of the ovaries is poorly differentiated and immunohistochemistry is not specific. Ovarian cancer with neuroendocrinization is relatively rare and there are few relevant descriptions in the literature. In a previously reported case, a patient had peritoneal recurrence of high-grade serous ovarian carcinoma with tumor cell components expressing neuroendocrine markers but lacking the morphological features of neuroendocrine differentiation (25). A case of simultaneous ovarian neuroendocrine and endometrial serous carcinoma has also been reported, but the ovarian tumor was confirmed to be metastatic from the endometrial serous carcinoma by gene sequencing (26). Schultheis *et al* (27) showed that ovarian metastases could be confirmed to originate from endometrial cancer by genetic testing of pathological tissues of co-occurring endometrial and ovarian cancers and found that the vast majority shared common ancestral clones. Karpathiou *et al* (26) argued that caution should be exercised when interpreting immunostaining results in poorly differentiated carcinoma because the expression of neuroendocrine markers does not necessarily indicate a tumor of neuroendocrine cell origin. Instead, it represents a form of tumor progression. In addition, the clinical manifestations of ovarian metastases and primary cancers differ. The classic criteria for ovarian metastasis in endometrial cancer include bilateral multinodular small ovarian involvement, large endometrial tumors with deep muscularity and vascular invasion and tubal lumen involvement. By contrast, primary ovarian cancers are unilateral, large and have different morphological types. In the present study, the ovarian biopsy pathology of the patient showed a low-grade carcinoma with local neuroendocrine differentiation. The clinical manifestation was a large-volume unilateral tumor. The patient also had cervical neuroendocrine carcinoma and endometrial cancer. Therefore, poorly differentiated ovarian carcinomas can be primary or metastatic. The source of ovarian cancer cannot be identified by pathology and immunohistochemistry alone and it needs to be confirmed by gene sequencing if it is to be further confirmed. In addition, genetic testing can determine whether a patient has genetic syndromes. Unfortunately, due to the poor financial status of the patient, this examination was not performed. The absence of genetic testing is a limitation in this case, but this patient has no family history of hereditary tumor syndromes, which can basically rule out genetic factors. In addition, the lack of MRI scans before breast cancer surgery was also a limitation in the present case.

The patient had multiple primary cancers simultaneously, with multiple and complex pathological types, making the choice of a treatment plan more difficult. Due to the large cervical cancer mass with lymphocytic metastasis, hypodifferentiated ovarian and bilateral breast cancer without axillary lymph node metastasis, it was decided to perform neoadjuvant chemoradiotherapy to shrink the gynecological tumor for surgery and simultaneously treat the bilateral breast cancer at the same time. Considering the pathological type of the patient, the decision was made after multidisciplinary consultation and discussion of albumin, paclitaxel and carboplatin combined with bevacizumab chemotherapy and concurrent pelvic radiotherapy. Following neoadjuvant therapy, gynecological surgery was performed and she was diagnosed with endometrial cancer. The original chemotherapy regimen is also applicable to endometrial cancer. Subsequently, three cycles of chemotherapy and radical mastectomy were performed. Currently, the patient has been reviewed regularly and no metastasis or recurrence has been observed.

In summary, MPMN is common. The reasons for its occurrence are multifaceted and include genetic, physical and environmental factors, cancer inducers caused by chemotherapy or radiotherapy, or decreased immune function (28). Patients with MPMN have obvious genetic factors and genetic abnormalities may be the cause of multiple cancers (29). Abnormal DNA mismatch repair is also associated with MPMN (29-31). MPMN can occur at any age but is more likely to occur in middle-aged and elderly individuals. The incidence of MPMN is higher in men than in women (32). When a patient is suspected of having an MPMN, a comprehensive physical examination should be performed to detect and treat other potential cancers in a timely manner. The principle of treatment for multiple cancers is to develop an individualized treatment plan based on the specific situation of the patient, including comprehensive treatments such as surgery, radiotherapy, chemotherapy and targeted therapy.

Currently, there is no standard treatment protocol for multiple cancers. Most literature on multiple cancers is presented in the form of case reports that can be used by oncologists to learn from each other. There remain a number of forms of multiple cancers or successful cases that are not widely known. A multi-cancer website could be established for oncologists, in order to deepen the understanding of multiple cancers and learn from each other's experience in treatment, so that multi-cancer can be diagnosed and treated early and prognosis improved.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

JG and LH drafted the manuscript and conceived the study. LZ, CX, MJ and GZ were responsible for collection and analysis of case data and literature. JG provided financial support. MJ and GZ confirmed the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of this case report and its accompanying images

Competing interests

The authors declare that they have no competing interests.

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